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DEXAMETHASONE THERAPY IN BRONCHIAL ASTHMA

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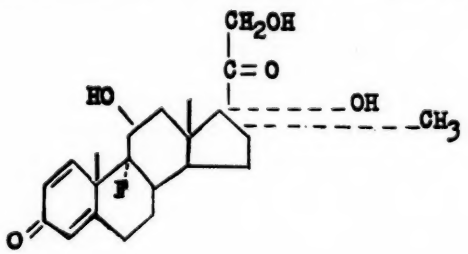
WE have been evaluating the effectiveness of various types of corticosteroids in patients with bronchial asthma since the Fall of 1949. The ideal steroid hormone for this disease should suppress its manifestations without producing undesirable side effects. More recently, an interesting compound, dexamethasone (16 ∝-methyl 9 ∝-fluoroprednisolone) was



16∝-methyl, 9∝- fluoroprednisolone

synthesized by Arth and his co-workers.[1,2] Boland[3] carried out preliminary studies of the anti-rheumatic potencies of hydrocortisone analogues which were methylated at carbon sixteen. One of these methylated com-

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TABLE I. DIAGNOSIS, PREVIOUS STEROID THERAPY AND REASONS FOR DECADRON THERAPY (FORTY-ONE PATIENTS)

Diagnostic Groups	Previous Steroid Therapy		Reasons For Giving Decadron®		
	Yes	No	Evaluation of Drug and Therapy	Excessive Weight Gain on Previous Steroid	Inadequate Clinical Improvement on Previous Therapy
(a) Chronic bronchial asthma	16	4	6	3	11
(b) Perennial—seasonal—pollen asthma	2	2	2	—	2
(c) Bronchial asthma and hay fever	3	2	3	—	2
(d) Bronchial asthma and nasal polypi	3	—	2	—	1
(e) Bronchial asthma and eczema	2	—	2	—	—
(f) Status asthmaticus	—	1	1	—	—
(g) Bronchial asthma and diabetes mellitus	1	1	1	—	1
(h) Bronchial asthma and obesity	4	—	1	3	—
Total	31	10	18	6	17

pounds (dexamethasone, MK-125, Hexadecadrol, Decadron®*) was found to promise greater clinical efficacy and safety. Bunim and others[4] studied its adreno-cortical, metabolic and early clinical effects in eighteen patients with rheumatoid arthritis for periods up to twelve weeks. Spies and others[5] recently reported the high degree of effectiveness of this new compound in eleven patients with various steroid responsive diseases. This was a short term study employing relatively high dosages.

The purpose of this report is to present our clinical experience with the use of this interesting drug in patients with severe bronchial asthma. Metabolic and physiological studies were not carried out in these patients.

MATERIALS AND METHODS

Dexamethasone was given to forty-one patients with chronic bronchial asthma for periods of from two weeks to seven months. The diagnostic grouping of these patients is shown in Table I.

There were thirty-one women and ten men in the group with ages ranging from twenty-four to seventy-one years. There were eight patients in the third decade, seven in the fourth, eleven in the fifth, eight in the sixth, six in the seventh and one in the eighth decade; thus 63 per cent of the patients were above the age of fifty years.

During the first two months, the patients were seen at one to two week intervals and subsequently, less frequently. Pertinent system review and physical examination were carried out each time. Urine and stool examinations were done in most patients before and during therapy. Complete blood counts, serum determinations for sodium, potassium, chloride, non-protein nitrogen, glucose and carbon dioxide combining power and roentgenological examinations of the chest and gastrointestinal tract were carried out when clinically indicated.

*Decadron® was kindly supplied by Dr. Elmer Alpert of the Merck, Sharp & Dohme Research Laboratories.

In our group of forty-one patients, thirty-one were on either prednisolone or triamcinolone before dexamethasone was started (Table I). The remaining ten patients had severe enough disease to warrant steroid therapy. The reasons for dexamethasone therapy in each group are also shown in Table I.

TABLE II. PREVIOUS STEROIDS AND DECADRON (THIRTY-ONE PATIENTS)

Group and No.†	Age	Sex	Previous Steroids			Decadron®			
			Duration	Recent Steroid	Maint. Dose mg/d.	Initial Dose mg/d.	Duration of Rx	Maint. Dose mg/d.	Ratio*
(a) 1	54	M	4 mos.	Triam.	5.5	1.6	6 mos.	1.0	5
5	65	F	9 mos.	Triam.	4	0.8	4 wks.	0.8	5
8	30	F	10 mos.	Triam.	1.5	0.8	6 mos.	0.5	3
9	31	F	10 mos.	Triam.	5.5	2.0	3 mos.	1.75	3
12	35	M	32 mos.	Triam.	6	1.2	6 mos.	2.0	3
13	26	F	3 mos.	Triam.	2	0.4	5 mos.	0.8	2.5
21	40	M	3 yrs.	Triam.	4	2.0	6 mos.	2.0	2
22	62	F	5 yrs.	Triam.	4	0.8	6 mos.	0.75	5.3
23	43	F	3 yrs.	Triam.	2	1.6	6 mos.	0.25	8
24	49	F	2 yrs.	Triam.	5	1.6	6 mos.	0.5	10
25	60	M	3 yrs.	Triam.	4	2.0	2 wks.	2.0	2
26	54	M	2 yrs.	Prednis.	20	0.5	6 mos.	0.5	40
29	65	F	4 yrs.	Triam.	4	1.0	6 mos.	0.75	5.3
31	22	F	2 yrs.	Triam.	6	2.0	5 mos.	1.0	6
43	36	M	4 yrs.	Prednis.	20	2.0	2 mos.	0.25	80
44	24	F	3 yrs.	Triam.	2	2.0	2 mos.	0.75	2.6
(b)28	32	M	4 yrs.	Triam.	4	1.6	5 mos.	0.75	5.3
32	40	F	2 yrs.	Prednis.	10	2.0	4 mos.	2.0	5
(c)27	45	F	2 yrs.	Prednis.	7.5	1.6	5 mos.	0.5	15
35	49	F	1 mos.	Prednis.	10	1.0	2 mos.	1.0	10
45	53	F	1 yr.	Triam.	2	1.0	2 mos.	1.0	2
(d) 2	44	F	1 yr.	Triam.	4.5	1.6	10 wks.	0.6	7.5
4	34	F	5 yrs.	Triam.	12	3.2	3 wks.	3.2	3.7
6	56	F	9 mos.	Triam.	3	0.8	7 mos.	0.25	12
10	43	F	9 mos.	Triam.	8	2.4	1 mos.	1.4	5.7
(e)20	27	F	4 mos.	Triam.	4	1.6	6 mos.	0.25	16
37	50	F	3 yrs.	Triam.	4	1.0	2 mos.	0.5	8
42	45	F	2 yrs.	Triam.	4	0.75	3 mos.	0.5	8
(f) 19	29	F	9 mos.	Triam.	4	0.8	6 mos.	0.5	8
30	29	F	2 yrs.	Prednis.	5	1.6	3 mos.	1.6	3
(g)15	50	F	3 yrs.	Triam.	4	0.8	2 wks.	0.8	5

†Please see Table I.
*Ratio: Maintenance doses of Decadron to previous steroids.
Triam. = Triamcinolone.
Prednis. = Prednisolone.
Mos. = Months.
Wks. = Weeks.
Yrs. = Years.

The initial daily dose of dexamethasone used in the majority of the patients varied from one-fourth to one-half by weight of the dose of the previously used triamcinolone. No definite pattern was followed in the patients who had previously taken prednisolone. Table II represents details of previous steroid therapy and the treatment with dexamethasone including comparison of maintenance dosages. A moderate restriction of dietary salt was found necessary in a very few patients. Table III represents the mean maintenance dosages for the previously used steroids as compared to dexamethasone.

OBSERVATIONS

A significant observation was the increase in appetite and weight gain noted in the first one to three weeks of treatment in the majority of the patients. There was no anorexia or weight loss noted. Thirteen patients gained five to ten pounds of weight and seventeen gained over ten pounds during therapy. Thus moderate to marked weight gain was noted in 73 per cent of these dexamethasone treated patients. Our observations indicate that this weight gain was due to increased appetite and food intake rather than edema fluid.

TABLE III. COMPARISON OF MEAN DOSAGES IN THIRTY-ONE PATIENTS (DECADRON® TO PREVIOUS STEROIDS)

	Mean Maint. Dose (mg/d.)	Decadron® Mean Maint. Dose (mg/d.)	Ratio	Number of Patients
Triamcinolone	4.3	1.0	4	25
Prednisolone	12.0	0.85	14	6

Four patients (10 per cent) showed evidence of mild or moderate degree of ankle edema. Three of these patients (Nos. 6, 9, 12) responded to oral chlorothiazide therapy with disappearance of their ankle edema.

One patient (No. 25) had symptoms of reactivation of his old duodenal ulcer two weeks after the start of the drug. Another (No. 5), who previously had mild gastrointestinal symptoms, developed hematemesis and melena four weeks after dexamethasone was started; no ulcer could be demonstrated by upper gastrointestinal series. A third patient (No. 2) experienced a marked increase of her upper gastrointestinal symptoms while her asthma was fairly well controlled. She remained on the drug for ten weeks. Dexamethasone was discontinued in these three patients.

The drug was omitted in three other patients because of the following observations: recurrent hypertension (patient No. 3), persistent recurrent asthmatic attacks and extreme weakness (patient No. 4) and recurrent infections with marked weight gain (patient No. 9). Thus the drug was discontinued in a total of six patients. One additional patient failed to return to the clinic. However, there was a good response of her chronic bronchial asthma at the end of the first month to dexamethasone therapy.

Two patients in the group were diabetic. One of them had lost weight and complained of nausea, vomiting and weakness prior to starting Decadron therapy. She was discovered to have diabetes mellitus two weeks after onset of therapy with Decadron®; however, it is believed that her symptoms at the outset were due to diabetes mellitus which was initially overlooked. The drug was discontinued when diabetes was recognized, but it cannot be implicated in the etiology of her diabetes mellitus (patient

No. 15). The second patient with moderately severe diabetes mellitus (patient No. 35) required increased dosages of insulin two months after the start of therapy. This was determined to be attributable to a severe lower respiratory tract infection. With antimicrobial therapy and an

TABLE IV. SYMPTOMS AND SIDE EFFECTS BEFORE AND AFTER DECADRON (FORTY-ONE PATIENTS)

Before Decadron®					After Decadron®			
Severe	Moderate	Mild	None		Severe	Moderate	Mild	None
—	—	1	40	Edema	—	1	4	36
—	—	3	38	Abdominal pain	1	2	3	35
—	1	1	39	Diabetes mellitus	2	—	—	39
—	—	2	39	Acne	—	1	3	37
—	3	10	28	Cushing-like appearance	—	3	14	24
—	3	2	36	Infection	—	5	2	34
—	—	2	39	Headache and/or vertigo	—	—	2	39
—	—	1	40	Muscle weakness	1	—	1	39
—	3	4	34	Upper G. I. symptoms	2	2	7	30
				Ulcer				
—	—	1	40	Clinical	2	—	—	39
—	—	1	4	By G. I. series	—	—	—	4
				Bleeding				
—	—	—	41	Occult	—	—	1	40
—	—	—	41	Frank	1	—	—	40
				Hair				
—	—	1	40	Overgrowth	—	1	—	40
—	—	—	41	New growth	—	1	—	40

increase in Decadron® dosage, the infection subsided, the bronchial asthma was adequately controlled and his insulin requirements returned to pre-infection levels.

Two patients complained of extreme weakness and were given supplemental potassium chloride along with additional potassium in the form of orange and cranberry juices. However, there was no decrease of serum potassium.

There were no rashes, ecchymosis, jaundice, osteoporosis or pathological fractures noted. No essential changes of blood pressure were observed in the whole group, except the previously mentioned patient with recurrent hypertension. Five of the ten patients who were emotionally depressed at the onset of treatment improved while taking the drug. There were no untoward central nervous system changes observed.

The incidence of Cushingoid appearance, infection, and so forth, is shown in Table IV as symptoms and side effects before and after dexamethasone.

RESULTS

Among the forty-one asthmatic patients treated with dexamethasone, the response was considered good in thirty-two patients (79 per cent) and fair in seven patients (16 per cent). In two patients (5 per cent) in whom the drug was discontinued because of early complications, the response of their bronchial asthma could not be evaluated.

It is of considerable interest that most of the patients with good results demonstrated weight gain as previously mentioned.

COMMENTS

Dexamethasone was found effective in the treatment of forty-one patients with bronchial asthma. Its appetite-stimulating effect and weight gain is a definite therapeutic advantage in many patients requiring steroid therapy. In fact, it may conceivably prove of life saving value in the severely debilitated, anorexic, malnourished subject who does not present any specific indication for steroid therapy.

It was thought that the same calculated risk and precautions should be taken for the use of dexamethasone as with other steroids in the presence of gastrointestinal symptoms and diabetes mellitus. Although difficult to evaluate in a series of this moderate number of cases, the minor side effects—namely, Cushingoid appearance, edema, recurrent hypertension (one patient), changes in hair growth, infection, et cetera (as shown in Table IV)—did not seem to be much greater than with the steroids we have previously studied.

The average maintenance dose required for the control of these asthmatic patients was about 1.0 mg daily. It is of interest that our therapeutic ratio of 1:4 (dexamethasone-triamcinolone) is considerably higher than the 1:6 to 1:10 ratios, largely in rheumatoid disease, previously reported by other investigators. The above comparisons suggest a more sensitive response in other types of diseases studied in contrast to our patients with bronchial asthma.

SUMMARY

Dexamethasone (16 α-methyl 9 α-fluoroprednisolone) was given to forty-one patients with bronchial asthma for periods up to seven months. The clinical response, symptoms and side effects, and comparison of dosage with previously used steroids have been discussed. In addition to the effectiveness of dexamethasone in suppressing the manifestations of bronchial asthma, the marked increase in appetite and weight were of particular interest. These factors may be of significance in selecting the appropriate steroid agent for patients requiring such therapy.

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TREATMENT OF SEVERE ALLERGIES WITH DEXAMETHASONE

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AN ABUNDANT literature testifies to the efficacy of synthetic adrenal steroids in the management of many types of respiratory and dermatologic allergies which are inadequately controlled by standard measures. Although the mechanism of action of these agents in allergy is poorly understood, it is considered unlikely that they interfere directly with the antigen-antibody cycle. There is evidence[1] that allergic phenomena occur as part of a physiological stress situation to which the adrenal cortex responds with heightened secretory activity. Presumably, if this response is inadequate, the exogenous source corrects the relative insufficiency.

Steroid therapy in allergy should be confined to patients who are not sufficiently benefited by more conservative measures. Usually the steroids are administered only intermittently for short-term emergency situations.[2] However, there have been some reports[3-6] of attempts to maintain patients with intractable allergies on continuous, low-dosage steroid therapy for relatively long periods of time. If the patients are selected carefully and supervised closely, this regimen is not unduly hazardous and its value may be considerable.

Prednisone and prednisolone became the agents of choice in allergy because they are unlikely to produce certain undesirable effects of cortisone and hydrocortisone. In an attempt to increase the efficiency of steroid therapy, other analogues have been synthesized recently. Heightened therapeutic activity without a proportionate rise in side reactions was sought. Deronil (dexamethasone), a 16-methyl derivative of prednisolone, apparently meets this requirement. The milligram-for-milligram potency is at least six times that of prednisolone and thirty times that of hydrocortisone. There are favorable reports of its use in arthritic disease,[7-14] inflammatory disorders of the eye,[15-17] some allergies,[13-18] and the nephrotic syndrome.[19] Most of these investigators commented on the relative absence of side effects. Metabolic studies[20] indicate that the steroid hormone apparently has no adverse effect on electrolyte balance.

METHOD

Patients were selected with intractable, usually chronic, bronchial asthma for the preliminary clinical trial with Deronil*. Some also had seasonal or perennial allergic rhinitis or allergic dermatoses. Also included were a few patients with exceptionally severe allergic dermatoses but without respiratory involvement. In this group of thirty patients, standard anti-allergic

*Deronil was supplied for this study by George Babcock, Jr., M.D., of the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

management had not resulted in adequate relief of symptoms. A second group of nine patients consisted of those who experienced mild or moderate allergies which were reasonably well controlled under previous therapy, and who also had severe and unrelieved arthritic disease (Table I).

TABLE I. INDICATIONS FOR DERONIL

Indication	Patients' Sex and Age Range	Weeks of Therapy
Bronchial asthma	4M, 3F, 44-76 years	(4*) 24-28½
Bronchial asthma and allergic rhinitis	4M, 10F 12-66 years	21-28½
Bronchial asthma and allergic dermatoses	1M, 1F, 41, 47 years	25, 28
Bronchial asthma and chorioretinitis	1M, 1F, 41, 69 years	27, 28½
Bronchial asthma and psoriasis	1F, 39 years	28
Allergic rhinitis	1F, 49 years	27
Allergic dermatoses	3M, 27-61 years	(2*) 15, 21
Bronchial asthma and arthritis	2F, 34, 64 years	18, 23
Allergic rhinitis and arthritis	3F, 53-70 years	20-25
Allergic dermatoses and arthritis	3M, 1F, 39-60 years	15-23
Summary	16 male, 23 female average age: 51 years	average: 24 (* omitted)

The offending allergens were identified in nearly all patients. Pollens, dust, molds, bacteria, and animal dander affected the patients with respiratory allergies; *rhus* or industrial allergens caused the cases of allergic dermatitis. The usual procedures for hyposensitization were carried out.

Treatment was initiated with one 0.75 mg tablet of Deronil four times daily. Two patients who failed to respond within three or four days then received twice this amount. Dosage was gradually reduced until the maintenance level, usually two tablets daily, was established for each patient. If there was an exacerbation of symptoms, dosage was increased temporarily and reduced again. Patients were treated for an average of twenty-four weeks and some now have received the drug continuously for almost seven months.

RESULTS

The patients suffering from bronchial asthma, allergic rhinitis, and/or allergic dermatoses responded very well to Deronil. Relief was considered to be excellent in twenty of these twenty-seven patients, good in four, and fair in two. A highly emotional patient with persistent urticaria failed to benefit, and discontinued therapy after two weeks because of insomnia.

Symptoms of bronchial asthma were greatly relieved in the two patients with chorioretinitis. Both were referred to an ophthalmologist, who reported considerable improvement of the eye disorder. The patient with bronchial asthma and psoriasis experienced an excellent response in the former condition and some improvement in the latter.

The nine patients with arthritis and controlled respiratory or dermatologic allergies reported good or excellent relief of all symptoms when Deronil was added to the regimen.

The side effects of therapy with Deronil are summarized in Table II. Those which occurred in more than one patient were mild edema apparent-

TABLE II. SIDE EFFECTS OF DERONIL

Side Effect	Patients' Sex and Age Range	Weeks of Therapy
Slight fluid retention	3F, 57-64 years	23-28
Occasional headache	1M, 2F, 49-52 years	27-28½
Slight insomnia	2M, 61, 76 years	21, 28½
Severe insomnia	1M, 54 years	2*
Occasional fatigue	1F, 50 years	27
Slight "cramps"	1F, 41 years	28
Slight "heartburn"	1F, 66 years	25
Summary	4 male, 8 female average age: 57 years	average: 26 (* omitted)

ly due to fluid retention (which was easily relieved by diuretics), headaches, and insomnia. These effects usually were transient and in only one patient (noted above) was it necessary to discontinue therapy. Despite the fairly long duration of administration, none of the more serious side effects which are encountered occasionally during steroid hormone therapy were seen in this series. Blood pressure and hemoglobin levels were checked periodically in all patients and no significant variations were noted.

The average age of patients who experienced an untoward reaction (fifty-seven years) was slightly higher than the average age of the series as a whole, (fifty-one years) but no other significant differences were apparent.

SUMMARY

Twenty-seven of thirty patients suffering from intractable bronchial asthma, seasonal or perennial allergic rhinitis, and/or allergic dermatoses experienced marked relief of symptoms with dexamethasone (Deronil). The steroid hormone was administered in divided doses of 3.0 mg daily reduced to 1.5 mg daily for approximately six months. Nine patients with mild or moderate allergic involvement and arthritic disease were also benefited. The side effects experienced by more than one patient were mild, easily reversible fluid edema, occasional headaches, and insomnia. No serious adverse reaction occurred in any patient.

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VARIATION AND NORM

Biological variation is the antithesis of both the Platonic Ideal and the stable Norm since a variable absolute is by definition a contradiction of terms—nonsense. Yet we still quite generally fail to recognize this fact. Striving for specious simplicity we tend to exclude variation from our thinking, either by ignoring its existence or by mathematically compressing it into a rigid, artificial mold. We tabulate the anatomical and physiological dimensions of our fellow mortals and, after averaging them, we correct them to what we call "ideal man," never blushing that we know nothing about "ideal man" except that he has a body surface of 1.73 square meters and an ideal basal metabolic rate of some 40 calories per square meter per hour. We measure his cardiac output, his respiration, many functions of his glands and kidneys, and even of his psyche, and in our tables we presumptuously apply a correction factor to women to bring them up to the male's ideal measurements, without asking ourselves, Whence comes this creature of statistical perfection, this paradigm, this prototype, to whom we approximate real men (and women) by an easy mathematical correction?—HOMER W. SMITH, "Plato and Clementine," Morris Herzstein Lecture (III), University of California, December 6, 1946.

DEXAMETHASONE: A NEW CORTICOSTEROID—ITS EFFECT IN ALLERGIC DISEASE

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A decade of corticosteroid therapy has seen many synthetic modifications of cortisone, each of them useful in the symptomatic management of severe allergic states. The search for active compounds with greater anti-inflammatory activity and less secondary hormonal effects continues. Dexamethasone is one of the most recent additions to this growing list of synthetic compounds. The present report reviews almost one year's clinical experience in the use of this newly developed steroid.

Dexamethasone* is 9-alpha-fluoro-6-alpha-methyl prednisolone. Its anti-inflammatory activity in animals is reported to be six and one-half times that of prednisolone, and thirty to forty times that of hydrocortisone.[1] Other workers have observed that in the intact or adrenalectomized animal, it is 200 times as potent as hydrocortisone as far as granuloma inhibition is concerned, while only twenty times as potent in relation to glycogen deposition.[2] This finding has suggested that dexamethasone may have less effect on carbohydrate metabolism than other corticosteroids in proportion to its greatly enhanced anti-inflammatory activity. The 16-alpha-methyl function eliminates the sodium-retaining properties of 9-fluoro steroids to the extent that the electrolyte regulating activity of dexamethasone is almost immeasurable.[3] As a result, this new compound is the most potent anti-inflammatory steroid yet found which is suitable for clinical use.[4,5,6]

THERAPEUTIC EFFECTS

Dexamethasone was administered to a total of 132 patients with various allergic problems of a severity justifying the use of corticosteroids. Some patients had more than one manifestation of allergy, accounting for the greater number listed in the accompanying table (Table I). In this series there were thirty-two patients with chronic bronchial asthma, thirty-four with pollen hay fever, twelve with chronic urticaria or angioneurotic edema, six with eczematous contact-type dermatitis, and six with severe

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*Dexamethasone used in this study was Decadron® supplied through the generosity of Dr. Nicholas Capeci, Department of Clinical Research, Merck Sharpe & Dome, Inc., West Point, Penn.

non-seasonal allergic rhinitis. Sixteen patients received the drug because of acute allergic reactions to drugs.

The ages of the patients ranged from five to sixty-nine years, with nine patients less than 12 years of age. The periods of continuous administration varied from three days to eight and one-half months, with thirty patients receiving dexamethasone continuously for more than six months.

TABLE I. THERAPEUTIC EFFECTS OF DEXAMETHASONE

Condition Treated	Number of Patients	Results		
		Good	Fair	Poor
Bronchial asthma	75	55	15	5
Atopic eczema	32	22	6	4
Seasonal hay fever	34	22	8	4
Urticaria or angioneurotic edema, chronic	12	9	3	0
Contact eczema (acute)	6	6	0	0
Rhinitis (perennial allergic)	6	3	3	0
Drug reactions (acute)	6	6	0	0
Totals	171	123	35	13

The therapeutic response induced by dexamethasone in adequate doses was similar to that experienced with cortisone, hydrocortisone, and their successive modifications. In most cases an initial daily dose of 2.0 to 4.0 mg proved successful in establishing control of symptoms in a period of twenty-four to seventy-two hours. In the face of more severe difficulty, an increase in the daily dose to as much as 8.0 mg daily was required in some instances to produce the anticipated effect. A small number did not achieve a satisfactory response even with this dosage, and were classified as failures. It is possible that control could have been achieved with higher doses.

In those who required continuation of steroids over a longer period of time, suppression of symptoms was usually maintained with doses of 0.5 to 3.0 mg daily. Failure in this range prompted us to try another compound rather than to carry the patient on higher doses of dexamethasone.

The opportunity presented itself to compare the so-called "maintenance" requirements of dexamethasone with prednisone or prednisolone in a number of patients. On a milligram basis, dexamethasone would appear to be from five to ten times as potent as the afore-mentioned analogues. It would be fair to say that a 0.75 mg tablet of dexamethasone usually achieved the same therapeutic effect as a 5 mg dose of either prednisone or prednisolone. In this series we noted several exceptions to this rule, usually in the direction of greater dexamethasone requirements. Less opportunity to compare dexamethasone with other synthetic analogues was afforded, but our findings at this time indicate that approximately 1.0 to 1.5 mg of dexamethasone is necessary to produce the equivalent effect of 4 mg of triamcinolone in patients with chronic bronchial asthma who must be maintained on steroids.

UNDESIRABLE EFFECTS

Unfortunately, in the case of corticosteroids, increased potency is not necessarily the most important objective to be achieved. The incidence of the so-called "side effects" to the therapeutic dose is the real index of superiority. The nature of these less desirable symptoms did not differ materially from those previously encountered with prednisone or prednisolone. However, the frequency of some of these effects appeared to vary.

Muscular cramps during dexamethasone therapy occurred less frequently. The incidence of gastro-intestinal disturbances also seemed reduced. As is true with most steroids, when epigastric distress was reported, the addition of anti-acids to the program was generally sufficient for control. The appearance of psychosis or marked personality change was not observed in any patient of this group. The syndrome of extreme fatigue, weakness, or drowsiness, observed in the use of triamcinolone[7] was not encountered in this series of patients receiving dexamethasone.

The two most frequently observed undesirable effects were the appearance of "moon-facies," and a gradual increase in body weight. Moon-face often appeared after short periods of administration, and persisted in some cases when doses were reduced to as little as 0.25 mg daily, but disappeared shortly after complete discontinuation of the drug. Weight gain was extremely common, and possibly was related to increased appetite stimulation with consequent increased food intake. While this might be desirable in the case of the debilitated or thin patient, most patients preferred not to gain weight. In some cases on prolonged therapy, increases of as much as twenty pounds were recorded. That this was not due to sodium and water retention was evidenced by failure to lose weight when diuretics and low sodium diets were prescribed. Where it was possible to discontinue steroids, a gradual return to previous weight levels almost invariably occurred.

The opportunity to observe the effects of dexamethasone on hyperglycemia presented itself in three cases. In one patient, who was receiving 20 mg of prednisone daily, with fasting blood sugar levels in the range of 175 mg, these levels fell to an average of 80 mg when transferred to 3.75 mg of dexamethasone daily. However, two other patients failed to show any appreciable differences in their elevated blood sugar levels when comparable therapeutic doses of either prednisone or dexamethasone were given.

Ecchymosis, stria, and hirsutism, were encountered about as often as with other corticosteroids. The relationship of osteoporosis to the use of dexamethasone could not be adequately assessed during the relatively brief periods of administration. The complaint of backache was recorded in three patients during therapy, and disappeared following discontinuation of the drug. In each of these cases, similar symptoms had developed while taking either prednisone or triamcinolone. No incident of compression fracture was encountered.

COMMENT

The clinical effectiveness of dexamethasone in allergic syndromes with doses much smaller than required with other corticosteroids confirms the laboratory findings previously noted. Effective therapeutic doses of dexamethasone, however, induce approximately the same range of less desirable steroidal effects as do prednisone, prednisolone, or methylprednisolone, but do not produce the fatigue syndrome of triamcinolone. The influence of dexamethasone on carbohydrate metabolism may be less in the experimental animal, but requires more careful study before this effect can be properly assessed in humans.

As the list of synthetic corticosteroids grows, there appears to be some tendency on the part of patients for selectivity of one compound over another. In this series, most patients found therapeutic doses of dexamethasone as satisfactory as any of the previously used steroids. On the other hand, in seventy-five patients with bronchial asthma, eleven preferred triamcinolone and three favored prednisone over the new steroid. While it is likely that any of the anti-inflammatory steroids will accomplish a similar result when given in adequate dosage, it is possible that one steroid may be better than another in a particular disease state or patient, aside from the occurrence of untoward effects. This possible development in corticosteroid therapy is worthy of consideration and study.

The use of any steroid in the control of allergic disease does not eliminate the necessity for identification and control of the underlying allergic factors responsible for the condition.

SUMMARY

Dexamethasone (9-alpha-fluoro-16-alpha-methyl-prednisolone) is an anti-inflammatory corticosteroid which effectively influences the course of a variety of common allergic syndromes.

The usual therapeutic response anticipated with corticosteroids may be attained with substantially smaller amounts of dexamethasone than with any other previously available compound. Initial daily doses in the present series were usually from 2.0 to 4.0 mg daily, with subsequent doses of 0.5 to 3.0 mg daily necessary to maintain improvement.

Therapeutic doses of dexamethasone produce approximately the same range of side effects as other synthetic steroids, but there appears to be some difference in their frequency. Moon-facies and weight gain are common during dexamethasone therapy. Gastrointestinal irritation and muscle cramps appear less often. Sodium and water retention or hypertention do not appear to be problems in dexamethasone use. Fatigue or weakness syndromes were not encountered in the present series.

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PATIENCE AND SELF-CONTROL

Meritorious patience presupposes relentless self-control. Here you have numerous ideas for experiments haunting you. Here you have the practical applications presenting themselves from all sides: the temptation to set aside temporarily the obscure and involved investigations is strong, imperative, tyrannical. You think you will come back to them later, and will fill the gaps after the work, more or less presentable, has been presented. In the meantime you conceal and hide them. It is so easy because the experts are very often satisfied with the apparent results. You are congratulated and may even cause some jealousies. But you know well enough that the question of filling the gaps will never come up again. The man who had not the strength to put the brake firmly, will never have the power required for going back. He has once let himself be carried away by the flood of ideas that beset him; having yielded, how could he resist later? And his work will be unstable because its foundations were too weak and too shaky; it will not stand the test of time. When it is necessary the experimentalist must be able to oppose a categorical, uncompromising and final no to his imagination. The experimentalist must possess full and entire self-control.—MAURICE ARTHUS: Philosophy of Scientific Investigation, Baltimore, The Johns Hopkins Press, 1943.

TREATMENT OF DERMATOLOGIC AND RESPIRATORY ALLERGY WITH DEXAMETHASONE

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SINCE the first corticosteroids were introduced in 1951, structural modifications have been made in an attempt to increase the milligram potency of these agents and reduce their toxicity. The newest steroid, dexamethasone, is a synthetic analogue of prednisolone which is six to seven times more potent than prednisolone and thirty-five times more potent than hydrocortisone.[1-7] Because of this greatly enhanced potency, the equivalent anti-inflammatory effect of the older steroids can be achieved with much lower milligram dosage.

METHOD

This series consists of twenty-six children and seventy-four adults suffering from dermatoses, rhinitis, bronchitis, or bronchial asthma of allergic origin. Most had been under our clinical supervision for some time before the trial with Deronil* was begun and had been treated with other types of medication. Other steroids had been used in nine patients. The patients with dermatoses had received topical therapy and occasionally antihistamines. Respiratory allergies had been treated with antihistamines and symptomatic therapy, and asthmatic patients had received aminophylline and ephedrine.

These patients were selected for treatment with Deronil because symptoms had persisted to some extent with other agents. Hyposensitization and standard antiallergic management was continued. Laboratory studies were made when indicated.

The period of observation ranged between one and sixteen weeks. Some patients received Deronil continuously while others, chiefly those with bronchitis and bronchial asthma, were given periodic courses of therapy for approximately one week every three or four weeks. Occasionally Deronil was used only to relieve an acute attack and then discontinued until again required.

We usually initiated therapy in adults with one or two tablets of 0.75 mg given three or four times daily for one or two days, and then gradually reduced by one tablet daily until the course was completed or a

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*Deronil (dexamethasone) was supplied by G. Kenneth Hawkins, M.D., of the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

TABLE I. RESULTS IN CHILDREN

Indication	Number of Patients	Age Range In Years	Clinical Effect			
			Excellent	Good	Fair	Poor
Atopic dermatitis	2 females	1-1½	1	—	1	—
Allergic bronchitis and rhinitis	1 male	2½	—	—	1	—
Allergic rhinitis	1 male	12	—	1	—	—
Asthma and atopic dermatitis	2 males	3-7	1	1	—	—
Asthma and rhinitis	7 males, 4 females	2-12	8	3	—	—
Asthma	7 males, 2 females	4-10	6	3	—	—
Summary	26	1-12	16 (61%)	8 (31%)	2 (8%)	—

maintenance dose of one tablet daily had been reached. This dosage was halved for children and quartered for infants. Generally, lower doses were used in patients with dermatoses than in those with respiratory allergies. We varied the amount and duration of therapy according to the severity of symptoms and made appropriate adjustments according to response.

RESULTS

The results of therapy in children are summarized in Table I and results among adults are summarized in Table II. Good or excellent results occurred in nearly all patients. The only therapeutic failure was in a patient with headaches of allergic origin, who later responded to hyposensitization and an appropriate diet.

Laboratory examinations yielded negative results. There were no toxic reactions to the drug and a gain in weight in a few patients was the only side effect observed.

TABLE II. RESULTS IN ADULTS

Indication	Number of Patients	Age Range In Years	Clinical Effect			
			Excellent	Good	Fair	Poor
Angioedema	3 females	42-62	2	1	—	—
Atopic dermatitis	2 males, 6 females	28-50	5	3	—	—
Allergic headache	1 female	55	—	—	—	1
Allergic bronchitis and rhinitis	3 females, 1 male	29-41	3	1	—	—
Allergic rhinitis	8 males, 8 females	29-51	4	12	—	—
Asthma and atopic dermatitis	1 male, 1 female	29-35	—	1	1	—
Asthma and rhinitis	5 males, 8 females	16-72	9	4	—	—
Asthma	17 males, 10 females	13-67	12	12	3	—
Summary	74	13-72	35 (47%)	34 (46%)	4 (6%)	1 (1%)

DISCUSSION

The following case summaries are typical of those in our series.

A patient with bronchial asthma had previously received 15 mg Meticortelone (prednisolone) daily with only partial relief. When 0.75 mg Deronil twice daily was added to this regimen, the chest became completely clear. He now takes Deronil, but has discontinued Meticortelone. Results are excellent.

A patient who had always complained of fatigue reported that he has had

more energy since therapy with Deronil was begun, and he appears to be very slightly euphoric.

A child with severe bronchial asthma, conjunctivitis, rhinitis, and otitis has had interrupted courses of therapy with Deronil. He is highly sensitive and has never received very high doses of antigens. Symptomatic medication has been a necessary part of therapy. He has a slight mooning of the face which is probably due to therapy but his clinical response has been good. The amount of improvement, although difficult to evaluate exactly, appears to be at least as good as (and probably better than) with other steroids.

In a patient with arthritis as well as allergic rhinitis, the sedimentation rate and eosinophil count approached normal, and there was regular clinical improvement of both nasal and joint symptoms.

We hesitated in giving Deronil to a patient with possible gastric ulceration, but he was so emotionally disturbed and incapacitated because of asthma that we decided to use the drug. Symptoms were controlled very well and bronchial spasm is present to only a minimal extent. There have been no gastric distress or other side effects from Deronil.

A patient who had been on Deronil for five months, with excellent results, had an abdominal operation during this period. There were no complications.

We have had a few patients whose asthma began late in life. Usually this is especially difficult to control, but our older patients have all responded well to Deronil.

In a woman suffering from severe bronchial asthma, allergic rhinitis, polyps, and dyspnea, who had previously received ACTH and Medrol (6-methylprednisolone), the response to Deronil was better than to either of the other steroids. Complete relief of nasal discharge occurred rapidly. The drug is now given periodically for acute episodes and provides excellent adjunctive therapy to hyposensitization. This patient is extremely nervous, but Deronil has not increased her emotional problem. She has been relieved of most of her clinical problems by combined antiallergic and steroid therapy.

Edema of the legs and bloating were reported by a patient who was started on rather high dosage of Deronil. The dose was reduced and diuretics were prescribed to relieve the apparent fluid retention. The clinical result was only fair. He had previously responded better to a combination of Meticortelone (prednisolone) and a tranquilizer.

A weight gain during therapy was observed in three patients. This followed a reported increase in appetite, apparently due to the tonic effect of the drug, and does not seem to have been caused by fluid retention.

In two patients, reduction of dosage to one or two tablets daily was followed by a recurrence of symptoms. At a slightly higher level of dosage the improvement returned and continued.

CONCLUSION

Deronil provides effective, safe, relatively inexpensive therapy for patients with acute or chronic respiratory or dermatologic allergies. Optimal results are achieved when small doses of Deronil are combined with hyposensitization and other standard antiallergic therapies, and this is an excellent regimen for long-term management.

This drug also appears to be safe for infants and children as well as for adults. We prefer to use several interrupted courses of therapy. Caution is used in administering the drug to very young children although results on an average of one-half tablet daily appear to warrant further trial in the treatment of pediatric allergies. Although relief is not always complete, it is significantly greater than could be obtained with other types of management.

There has been constant progress toward reduction of steroid side effects and we believe that, in this respect also, Deronil is superior to other steroids in current use. There have been no serious side effects in our patients. However, it is still necessary to be extremely careful in administering any steroid because each patient presents a different problem of diagnosis and therapy.

SUMMARY

Deronil (dexamethasone) was used for twenty-six children and seventy-four adults suffering from acute or chronic respiratory or dermatologic allergies. Excellent or good relief of symptoms occurred in sixty-nine adults (93 per cent) and in twenty-four children (92 per cent). There were no significant side effects.

When used in small doses with hyposensitization and other standard antiallergic measures, Deronil provides optimal control of allergic symptoms.

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9990 Northeast Second Avenue
Submitted May 7, 1959

THE USE OF DEXAMETHASONE IN THE TREATMENT OF ALLERGIC DISORDERS

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AS a result of the great benefit derived from the use of corticosteroids in the treatment of allergic diseases, continued efforts have been made to obtain newer steroids with improved therapeutic efficacy and without the undesirable side reactions. This paper deals with the use of a new corticosteroid compound, 9-alpha fluoro, 16-alpha methylprednisolone (Dexamethasone).*

METHODS

Dexamethasone was administered in divided daily doses to eighty-three patients over a period ranging from three weeks to eight months. All patients had the benefit of a thorough history, physical examination, and indicated laboratory and skin tests. A timed vital capacity was done in patients with pulmonary disease. Only those patients who did not obtain relief from the usual anti-allergic medications were given steroid therapy. In all cases, supportive therapy including bronchodilators, iodides, antihistamines and topical medications were used in an effort to minimize the dosage of dexamethasone required.

TABLE I. AGE AND SEX DISTRIBUTION OF PATIENTS TREATED WITH DEXAMETHASONE

Age	Number of Patients		
	Male	Female	Total
0-10	6	3	9
11-20	7	9	16
21-40	8	13	21
41-60	10	18	28
61 and over	4	5	9
Totals	35	48	83

The age and sex distribution of the patients is indicated in Table I. The ages varied from two years to sixty-seven years. Fifty-one of these patients had some form of bronchial asthma with or without other illnesses. The rest of the group consisted of eight patients with perennial allergic rhinitis, eleven patients with atopic dermatitis, ten patients with contact dermatitis, and three patients with chronic urticaria.

In the patients with bronchial asthma, fifteen had been on corticosteroid therapy for periods ranging from three months to three years, with a daily maintenance dose of 5 to 20 mg of prednisone or prednisolone. An attempt was made to maintain these patients on 0.5 mg to 2 mg of dexa-

*Supplied as Decadron® by Merck, Sharp and Dohme, Philadelphia, Pa.

methasone daily. The thirty-six patients who did not receive previous corticosteroid therapy were placed on 1 mg of dexamethasone every four hours for four days; 1 mg every six hours for three days; 1 mg after each meal and at bedtime for three days; then 1 mg after each meal for two days; then 0.5 mg after each meal and at bedtime for three days; then 0.5 mg after each meal for three days; then 0.5 mg after breakfast and supper for three days; and finally 0.5 mg after breakfast until cessation. This schedule was interrupted when necessary if symptoms recurred.

In the patients who did not have bronchial asthma, the dosage was started at 1 mg after each meal and at bedtime and the remainder of the schedule followed. In two patients with contact dermatitis, both of whom had poison ivy, it was necessary to increase the dosage to 2 mg every four hours to bring about a satisfactory response. Thirty patients required a maintenance dose of dexamethasone. Of these, two required 2 mg a day, five required 1.5 mg a day, thirteen required 1 mg per day, and ten required 0.5 mg per day.

RESULTS

Forty-nine of the fifty-one patients with bronchial asthma had good results from this treatment. It was noteworthy that the clinical improvement was more marked than the timed vital capacity measurements indicated. The two patients who did not respond were both severely ill, and responded to no medication until hypnosis was used by a consultant physician. Two in the group of patients had diabetes. One patient had to take two tablets of tolbutamide in place of the one he used prior to dexamethasone, the other patient was receiving insulin and no change in the insulin requirement was necessary.

The eight patients with perennial allergic rhinitis all did well. One of this group, a twenty-year-old woman, had been unable to tolerate prednisone, methylprednisolone or triamcinolone therapy because of dizziness, nausea and eye pain, but had no difficulty from dexamethasone.

The patients with atopic dermatitis, contact dermatitis and chronic urticaria were all well-controlled on dexamethasone.

SIDE EFFECTS

The most distressing side effect noted was epigastric pain, nausea or bloating. These symptoms were noted in eleven of the eighty-three patients treated. In most cases, these symptoms were relieved by antacid therapy, bland diet and taking the medication with milk after meals, but in two cases the drug had to be discontinued.

Fourteen of the patients noted a marked increase in weight while on treatment. Almost all patients noted an increased appetite while taking dexamethasone as well as a general sense of well-being. Two patients noted development of moon facies while on treatment. There was no

edema, hirsutism, significant changes in blood pressure or purpura noted in this group. Acne was noted in five patients, but they were also taking iodides at the time and therefore the steroid drug cannot be incriminated.

DISCUSSION

Dexamethasone was a valuable adjunct in the treatment of these allergic patients. The almost uniform good results can probably be attributed to the fact that all other modes of anti-allergic management were used in conjunction with steroid therapy. Results with other steroids have been similar in our experience. The most troublesome side effect with our patients on the various steroids has been epigastric discomfort, and this has also been seen with dexamethasone. The increased appetite and weight gain noted is a helpful factor in treating the poorly nourished, chronically ill patient, but is a distressing factor in the patient whose obesity is already an aggravant of his pulmonary disease.

CONCLUSION

Eighty-one patients have been successfully treated for periods up to eight months using dexamethasone with a low incidence of side effects. The dosage employed during treatment was smaller than that with other corticosteroids. No severe side effects were noted.

190 Hawthorn Street
Submitted February 27, 1959

EXPERIMENTATION AND "NORMAL" COURSE OF EVENTS

The specific design of experiments, the instruments employed and the paraphernalia needed, usually vary, depending on the problem under investigation. They may differ widely in the various sciences. Nevertheless, experimentation as a general method of inquiry involves at least two aspects which are common to all experiments. (1) Experimentation differs from mere observation in so far as it involves a deliberate disturbance of, or interference with, the "normal" course of events. (2) It assumes that every event in nature is determined by ascertainable conditions of its physical environment; that a duplication of these conditions entails a duplication of the event, and that changes in these conditions are followed by corresponding changes in the event. Experimentation, as distinguished from observation, consists in the deliberate and controlled modification of the conditions determining an event, and in the observation and interpretation of the ensuing changes in the event itself.—W. H. WERKMEISTER: An Introduction to Critical Thinking, pp. 618-619.

DEXAMETHASONE AS A SYMPTOMATIC AID IN HAY FEVER

Pilot Study

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THE clinical effectiveness of corticosteroid hormone therapy in allergic disorders is well established. In hay fever, its short term use must be reserved for supplementation of the generally effective immunologic technique of specific pollen hyposensitization therapy. Many valid considerations, of necessity, restrict the usage of these hormonal agents—for example, prevention of the hormonal side effects and the complications of non-specifically treated pollinosis.

The quest goes on for safer, more effective, minimal dosage steroids.

Dexamethasone (Decadron, Merck Sharp & Dohme) was made available for clinical evaluation of its effectiveness as a symptomatic adjuvant during the 1958 ragweed hay fever season. It was given chiefly to selected hay fever patients in the following categories: (1) those having received inadequate pre-seasonal specific ragweed hyposensitization therapy, representing, therefore, patients with sub-optimal dosage levels; and, (2) those requiring co-seasonal pollen hyposensitization because they reported for treatment after the onset of the ragweed hay fever season. In both classifications, it was used only to supplement the specific pollen therapy to provide additional symptomatic relief where necessary.

Of the entire series, seventeen had received steroid therapy previously. All of this number had received prednisone in an average dosage of 12 milligrams daily and in a dosage range varying from 10 to 20 milligrams daily. In addition, three of these patients had received triamcinolone. The average dosage was 11 milligrams daily with a range of 8 to 12 milligrams. One patient had also received methylprednisolone in a dosage of 4 milligrams daily.

The initial average daily dose of Decadron was 1.5 milligrams with a range of 0.75 to 2 milligrams daily. The average maintenance dose was 1.0 milligram with a range of 0.5 to 2 milligrams. The duration of therapy averaged seventeen days, with a range varying from seven to ninety days.

The evaluation of response to Decadron therapy was as follows. The average degree of improvement was between moderate and marked in the twenty-three hay fever patients. Three of these patients claimed very marked improvement and five attributed only slight benefit to this steroid. The differences interestingly did not appear to have been attri-

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Decadron® was supplied for this study by Dr. Nicholas E. Capeci, Merck Sharp & Dohme, West Point, Pennsylvania.

butable to dosage variation. A patient with neurodermatitis had moderate improvement on a dosage of 1 milligram a day which compared favorably with response previously achieved with 15 milligrams of prednisone daily or 12 milligrams of triamcinolone daily. A patient with bronchial asthma reported marked improvement on a maintenance dosage of 0.5 milligram of Decadron.

Patient preference was not particularly significant regarding choice of steroid hormone. However, one patient found Decadron inferior to prednisone and another preferred Medrol. A third patient preferred Decadron to both triamcinolone and prednisone. In the remaining patients no preference was admitted.

Undesirable hormonal effects were not seen or reported in the present series of patients treated for relatively short periods of time. None of the following were noted: (1) edema, (2) abdominal pain, (3) osteoporosis and/or pathological fracture, (4) ecchymosis, (5) diabetes mellitus, (6) abnormal hirsutism, (7) acne, (8) cushing-like appearance, (9) infection, (10) headache and/or vertigo, (11) muscle weakness, or (12) peptic ulcer.

None of the patients treated were hypertensive and in no instance was there any significant change in blood pressure following treatment.

Regarding weight changes, eighteen of the twenty-five patients were weighed prior and following the administration of Decadron. Twelve of the eighteen showed no change in weight. In the remaining six there was an average gain of 1.25 pounds with a range of 1.5 pounds to three pounds.

There was no notable change in the mental state of any of the patients while under Decadron therapy. Neither abnormal stimulation nor depression was observed.

Regarding carbohydrate metabolism, all but three of the patients had routine urinalyses before treatment, and in eight patients opportunity was afforded to recheck the urine after the patient had been on Decadron, and glycosuria was not observed in any of these patients.

From this small series in the selected group of ragweed hay fever patients, it appears that Dexamethasone is a satisfactory addition to our armamentarium where steroid therapy is indicated. It is possible to achieve additional symptomatic beneficial response in the low dosage range required by this medication. In the dosages used, side effects were not noted, and for the short periods used, it represents a useful supplement to our therapeutic agents.

6111 Jenkins Arcade Building
Submitted July 16, 1959

ALLERGIC REACTIONS DUE TO F D & C YELLOW NO. 5 TARTRAZINE, AN ANILINE DYE USED AS A COLORING AND IDENTIFYING AGENT IN VARIOUS STEROIDS

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AGENTS of coal tar origin are used to flavor and identify corticosteroids which today are used widely in the treatment of allergic reactions of all types.[1] It has been established that sensitization to drugs derived from coal tar is not infrequent.

This is a report on three patients who developed allergic-type reactions after ingesting: Case 1—dexamethasone (Decadron®) 0.5 mg tablets; Case 2—prednisolone (Paracortol) 5 mg tablets; Case 3—dexamethasone (Deronil) 0.75 mg tablets. Doses administered orally:

Case 1.—A sixty-six-year-old man suffering from severe bronchial asthma of an infectious type was advised to take 0.5 mg tablets of dexamethasone (Decadron). About forty minutes after he used his first prescribed 0.5 mg tablet of dexamethasone (Decadron) he developed severe generalized pruritus, itching of his tongue and uvula followed by generalized urticaria. His reaction progressed until many of his urticarial lesions were confluent.

His reaction was brought under control with the use of sympathomimetic drugs administered parenterally and in addition, Ephedrine sulfate gr ⅜ administered orally.

When tested, this patient reacted sublingually to 1 cc of a 1:1000 dilution of Tartrazine dissolved in triple distilled water.

His therapeutic response to undyed 0.5 mg tablets of dexamethasone (Decadron), graciously supplied by Merck Sharp and Dohme has been excellent.

Case 2.—A forty-nine-year-old orthopedic surgeon, known to be violently sensitive to drugs of mercurial and coal tar origin, developed a severe type of generalized reaction after using several 5 mg prednisolone (Paracortol) tablets to aid in controlling a generalized pruritus and a macular papular rash from which he was suffering due to exposure to Tincture of Merthiolate. Shortly after using several 5 mg prednisolone (Paracortol) tablets he developed severe generalized urticaria and in addition a localized edema of his lips, tongue and uvula. Exacerbations of all his previous symptoms occurred.

The prednisone (Paracort) 5 mg tablets do not contain Tartrazine. The patient is able to take prednisone (Paracort) 5 mg tablets without experiencing any untoward effects.

Case 3.—Dexamethasone (Deronil) 0.75 mg tablets were prescribed for a thirty-eight-year-old white woman collagen disease sufferer, also known to be sensitive to acetylsalicylic acid.

Shortly after this patient took her first tablet of Deronil, she experienced nausea and tingling of the mouth and tongue. She then developed generalized urticaria with vomiting associated with a severe headache. Her urticaria persisted for several days despite treatment with 1:500 Epinephrine in gelatine ad-

ministered intramuscularly and in addition, Ephedrine sulfate gr ⅜ and Benadryl HCl 50 mg orally.

When tested, this patient reacted to a 1 cc dose of a 1:1000 dilution of Tartrazine administered sublingually. The patient developed tingling of the tongue and lips with a sensation of burning. Later she developed mild edema of her upper lip and uvula with itching of her palate.

Tartrazine, also known as F D & C Yellow #5, is an aniline dye. It is a permitted primary certified food color used for coloring food, drugs and cosmetics; also as a dye for wool and silk. This dye, a potential sensitizing agent, is added to the following corticosteroids as a coloring and dosage identifying agent:

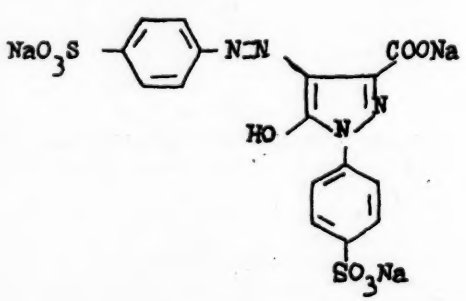
1. Dexamethasone (Decadron)[2] 0.75 mg tablets contain Guinea Green F D & C Green F D & C #1. dexamethasone (Decadron) 0.5 mg tablets contain F D & C Yellow #5 Tartrazine. Dexamethasone (Decadron) 0.75 mg and 0.5 mg tablets are manufactured by Merck Sharp & Dohme, division of Merck and Co., Inc., Rahway, New Jersey.
2. Prednisolone (Paracortol)[3] 5 mg tablets contain F D & C Yellow #5 Tartrazine. Prednisone (Paracort) 5 mg tablets contain no dye. Prednisolone (Paracortol) tablets 5 mg and prednisone (Paracort) 5 mg tablets are manufactured by Parke, Davis and Co., Detroit, Michigan.
3. Dexamethasone (Deronil)[4] 0.75 mg tablets contain F D & C Yellow #5 Tartrazine and F D & C Yellow #6 Sunset Yellow F C F. Deronil (Dexamethasone) 0.75 mg tablets are manufactured by Schering Corporation, Bloomfield, New Jersey.

Three of the above mentioned corticosteroid hormone preparations contain one dye in common, F D & C Yellow #5 Tartrazine,[5] a coal tar derivative manufactured by the Aniline Division of the Allied Chemical Corporation.

The Merck index[6]:

"Hydrazine yellow; F D & C Yellow #5 (when certified); trisodium salt of 3-carboxy-5-hydroxy-1-sulfophenylazopyrazole.

$C_{16}H_9N_4Na_3O_9S_2$; mol. wt. 534.39. C 35.96%, H 1.70%, Na 12.91%, S 12.00%.



Bright orange-yellow powder. Freely soluble in water. The aqueous solution is not changed by HCl but becomes redder with sodium hydroxide.

Use: It is a permitted coal tar color for coloring foods, drugs and cosmetics; also as a dye for wool and silk; commercially available."

SUMMARY

1. Tartrazine,[4] also known as F D & C Yellow #5, is an aniline dye. It is a permitted primary certified food color used for coloring food, drugs and cosmetics; also as a dye for wool and silk. It is commercially available. The pure dye contains not less than 85.0 per cent.

2. Tartrazine F D & C Yellow #5, an aniline dye, is used to color and identify: dexamethasone (Decadron) 0.5 mg tablets; prednisolone (Paracortol) 5 mg tablets and dexamethasone (Deronil) 0.75 mg tablets.

3. Tartrazine F D & C Yellow #5 is an aniline dye and known sensitizing agent.

4. Three cases of sensitivity to Tartrazine are reported.

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BASIC RESEARCH

Basic research is the qualitative and quantitative investigation of the laws and phenomena of nature; it requires the highest degree of individualism, knowledge and idea productivity, and it provides the spark that sets the complicated machinery of applied research in motion. However, as Vannevar Bush has stated, "The scientist doing basic research may not be at all interested in the practical application of his work."—PAUL DE HAEN, A report to the President, 1945—quoted in "Today and Tomorrow," *Med. Science,* 5:483-504 (April 10) 1959.

CLINICAL EVALUATION OF STOCK RESPIRATORY VACCINE IN THE TREATMENT OF BRONCHIAL ASTHMA

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IN bronchial asthma, the role of infection has been a controversial one, not so much from a clinical standpoint as from the search for an immunologic explanation of the phenomena.

We all agree, I think, that upper respiratory infections frequently precipitate attacks of asthma. The true explanation for this is still in doubt, and much confusion exists.

Many outstanding scientists in the field of medicine have made positive statements regarding the theory. Those who treat with vaccines give equally good reports as those who do not consider vaccines an effective therapeutic measure. Part of this confusion arises from semantic confusion in the use of the term "bacterial allergy."

The immunologist thinks of the term "bacterial allergy" as referring to an altered tissue reaction found in some bacterial infections. The prototype is tuberculosis with delayed inflammatory and even necrotic reaction to the local injection of bacterial cell extracts or culture filtrates. Such a reaction develops in a vast majority of individuals of the many species infected. It is not associated with humoral antibodies but can be transferred to normal animals by lymphocytes or fractions of lymphocytes.

The clinician thinks of a syndrome typified by asthma in children, starting as a "cold" with fever and cough; progressing into an asthmatic episode of several days to a week's duration; and clearing only to recur several times each winter. Or, he may see it typified by the onset at any age (but generally over forty) of steady perennial intractable asthma following influenza or "virus pneumonia." The skin tests to the common allergens are usually negative, but these patients have true allergic asthma with eosinophilia and complete reversibility of ventilatory abnormalities by epinephrine or steroids.

There is a third use of the term "bacterial allergy" which refers to diseases such as rheumatic fever, but this usage need not concern us here.

First, let us consider the subject of the delayed type of bacterial sensitivity from the immunologic point of view.

For the genesis of this state of sensitivity it is necessary for large numbers of intact bacterial cells to come in contact with focal inflammatory

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tissue. The lipoid fraction of the bacterial cell is essential and appears to act by inciting a local inflammatory response of macrophages (epithelioid cells). Intravenous injection of bacterial cells produces immunity, that is, precipitins, agglutinins and the Arthus type of sensitivity rather than the delayed type. The molecular configuration of the antigen may determine the type of sensitivity that develops. For example, Mayer[1] found that picrylchloride coupled to a globular protein evoked precipitins and anaphylactic sensitivity, but when coupled to procollagen, a fibrillar protein, evoked delayed sensitivity.

The mechanism of tissue damage in delayed sensitivity seems to be a direct cytotoxic action of the antigen on sensitized cells. The addition of antigen to a tissue culture explanted from a sensitized animal causes death of the cells.

The delayed reaction can be transferred to normal animals or to humans by lymphocytes and by fractions of lymphocytes obtained from lysed cells. The addition of antigen to suspensions of sensitized leukocytes releases into the supernatant saline solution a factor which transfers the sensitivity to normal animals.

Lawrence[2] postulates that the mechanism of the delayed sensitivity may be as follows: The leukocytes of sensitive individuals contain in their surface structure a type of cellular "antibody" or "transfer factor," with high affinity for antigen. Combination with antigen, possibly mediated by complement, results in the release of the cellular antibody-antigen complex and the cell is damaged in the process. The antigen-antibody complex disassociates, and other sensitive cells in the area may be damaged by the disassociated antigen. Non-sensitive cells attracted to the area may engulf the transfer factor (antibody), thereby becoming sensitized themselves. In this fashion, a progressive "chain reaction" is set in motion and continues until the antigen is exhausted.

It has been suggested that normal immunization is a biphasic process. The first stage is a production by the reticulo-endothelial cells of fixed cellular antibodies; it is associated with the delayed type of hypersensitivity. Dienes'[3] classical demonstration of delayed hypersensitivity to egg white in the first twenty-four to forty-eight hours after initial injection has been recently confirmed for other soluble antigens. The second stage of the process is the development of the antibody-producing cell into the plasma cell—with the release of large quantities of the antibody, which eventually appears in the serum as gamma globulin.

Further evidence in support of the concept that antibody production is a biphasic process is Good's[4] observation that individuals with congenital agammaglobulinemia can develop sensitivity to tuberculin, but they do not produce serum antibodies, and plasma cells cannot be found in their tissues. They appear to have as their primary disorder a failure of maturation of the reticulo-endothelial cell into the plasma cell.

As stated earlier, the delayed allergic reaction appears to be a direct cytotoxic action of the antigen on the sensitive cells, followed by the usual inflammatory response to tissue injury. Arteriolar dilatation with edema is not a prominent feature of the pathology and eosinophiles are not necessarily conspicuous.

Do bacteria (or bacterial proteins) and carbohydrates induce sensitivity of immediate type? The answer is, of course, yes. Avery and Tillet,[5] and Tillett and Francis,[6] have demonstrated many reactions to the pneumococcus and the pneumococcus specific polysaccharides, showing this antigen to be capable of producing typical anaphylaxis under appropriate circumstances. Dworetzky, et al,[7] have studied anaphylactic reactions to staphylococcus. The precipitin tests to streptococcic proteins and polysaccharides are well known and are the basis of Lancefield's[8] classification and typing of hemolytic streptococci. Countless other examples are known of precipitin and agglutinin response to bacterial antigens.

Bacterial antigens may also evoke reagins or skin-sensitizing antibodies. For example, Pappenheimer[9] has studied the non-precipitating reaginic antibody produced to diphtheria toxoid in animals and in man. Allergic reaction in humans to injections of this material is not uncommon and is identical to the reaction following the injection of pollen extract in individuals with hay fever.

Now we shall discuss the subject of bacterial allergy from the clinical point of view.

What is the evidence that bacterial sensitivity is the mechanism for human allergic disease states?

It is a very common observation that infection in the sinuses or the bronchial tree occurs at the same time as the allergic symptoms. The well-known antigenic activity of bacteria leads to the hypothesis that sensitivity to bacterial antigens was the mechanism for this allergic response. Evidence to support this hypothesis has been marshalled by Cooke,[10] and may be summarized as follows:

1. Examination of tissues removed at operation (for example, hyperplastic sinus mucosa) shows scattered bacteria deep in the tissue.
2. The symptoms are often relieved by treatment of infection by surgical drainage or antibiotics. Occasionally this relief is permanent and complete.
3. "Desensitization" with vaccines is often followed by improvement of symptoms.
4. Reproduction of symptoms is occasionally provoked by injection of minute amounts of vaccine.

Is this sensitivity of the immediate or the delayed type? While these two types of allergic reactions may overlap and may be fundamentally part of the same mechanism and an attempt to distinguish them may not be academically sound, it is practical to do so on clinical grounds, since the

mechanism of tissue damage is quite different. The delayed and the immediate types of allergy respond in totally different ways to symptomatic treatment. For example, consider the difference in management between urticaria and contact dermatitis.

Cooke[10] teaches that it is the delayed type because (1) skin tests to bacteria and bacterial extracts very rarely give immediate wheal and erythema reactions, but frequently give the tuberuclin type; (2) when a vaccine reproduces the symptoms, these symptoms appear twelve to forty-eight hours after the injection and last for several days.

However, the following observations suggest that the disease is the result of the immediate type of sensitivity.

1. Histological examination of nasal polyps or bronchial mucosa shows essentially identical pathology in "extrinsic" or "intrinsic" cases. The observed changes do not resemble the granulomatous lesion associated with typical delayed sensitivity of the tuberculin type.

2. These cases respond to epinephrine, aminophylline, and antihistamines in the same manner as pollen cases. This suggests that the mechanism of the reaction is the wheal and erythema type of allergy, with edema and smooth muscle spasms, rather than a tuberculin-type inflammation.

3. The family history often discloses relatives with typical extrinsic asthma.

4. The patients frequently have immediate and violent asthma after ingesting aspirin.

5. Positive skin tests of the delayed type to streptococci and staphylococci and other organisms occur as frequently as in allergic individuals. These reactions are customarily dismissed as being of no diagnostic value, signifying only past infection by the organisms. If delayed sensitivity were the mechanism of tissue damage in the clinical states of bacterial allergy, these tests would be expected to be significant. The fact that they are not is evidence that the sensitivity is not of the delayed type.

The twenty-four to forty-eight hour delay in the occurrence of symptoms following injection of vaccine may be due possibly to the necessity of lysis of bacterial cells before the antigen is available for reaction. Perhaps when free soluble antigen exists in sufficient quantity, the reaction then proceeds involving humoral antibody via the anaphylaxis mechanism. Cooke's[11] demonstration of reaction to proteoses of milk in milk-sensitive patients who reacted to the proteose but not to the whole milk on skin testing is an example of the idea that modification of the antigen in the body must occur before it can react.

Is this bacterial sensitivity a reaction to bacterial proteins? Is it the reaction to the products of bacteria, or is it a hapten reaction? Is it an immediate or delayed reaction? Some have ventured the theory that it might be a Shwartzman reaction. It may be a combination of two or more reactions. Many of these questions must remain unanswered until we

know the immunological reactions. Most of the evidence we have obtained is from clinical observation.

We will all agree, I believe, that bacterial asthma follows repeated upper respiratory infections. This is more evident in the northern states, where upper respiratory infections are more prevalent, and less pronounced in areas such as Florida, Texas, and Southern California. The interpretation of this evidence may differ. Some consider the nasal reaction which frequently precedes this type as nothing more than allergic response, triggered in the nose. If this were true then we would have an abundance of eosinophiles in the nasal secretion, which seldom occurs. It is almost universally found that the eosinophiles are replaced by large numbers of polymorphonuclear cells.

These upper respiratory episodes are more prevalent in the winter when infections are common. They are less prevalent in the summer when the bacteria or their virulence may be at a minimum. We are likely to speak of these as "colds," a term which is loosely applied. The so-called "cold" is a self-limiting disease usually lasting about seven days, but the nasal reaction in the allergic individual often lasts longer than seven days, persisting for two or three weeks or more. Are these upper respiratory infections in the allergic individual the same type we see in a non-allergic individual?

The so-called "cold" (upper respiratory infection) is thought to be due to a virus. Might it also be a sensitivity to virus? If so, where do the bacteria enter the picture? In all probability the virus lowers the resistance of the mucous membrane, allowing the secondary bacteria to take over. The closer one looks, the more confusing the picture.

Most allergists who use vaccine in the treatment of so-called "bacterial allergy," will agree that clinical improvement is made in this type of case. Some believe that the autogenous vaccine is superior to the stock vaccine, while others think the reverse is true.

I might say that I have used both and believe that in most cases the stock vaccine is more effective. If there is any doubt, I frequently use a combination.

Why should I be partial to stock vaccine? Let us look at the clinical evidence. In our clinic at the University of Oregon Medical School many cultures were taken from the posterior nasal pharynx, the nose, and the sputum, in a large group of individuals. One to four or more organisms were recovered, on the average. Repeated cultures from the same individual, a week later, seldom revealed the same organisms, yet the symptoms remained essentially the same. Confusion therefore arose regarding the type of autogenous vaccine to use.

If there were some particular focus of infection, such as the sinus, where the same organism was always present, the autogenous vaccine seemed the most logical to us; but this was seldom the case. The stock vaccine would therefore seem to cover a broader spectrum by including more organisms.

The success of vaccine therapy depends upon the choice of vaccine, dosage, and frequency of administration. By skin testing the individual, one can classify the extremely sensitive and use a greater dilution of vaccine.

It is preferable that the injections of vaccine be given twice a week in gradually increasing doses. Careful observations should be made for local and constitutional reactions, such as exaggeration of the symptoms within twelve to twenty-four hours after administration of the vaccine. If there is a large local reaction or if exaggerated symptoms appear within twenty-four hours, the next dose should be reduced or kept at the same level. Eventually one may obtain a maintenance dose, which can be repeated once a week or one every two weeks. This type of therapy should be maintained during the winter months rather than during the summer, since there will be less bacterial allergy at that time.

The question is frequently raised as to how long vaccine therapy should be continued. I can say from my own experience that when a decision to use vaccine has been made, I set a period of three years. At the end of that period if there is improvement, and there usually is, I discontinue vaccine therapy until there is a return of the disorder.

What are the values of bacterial testing with autogenous and stock vaccines? Here again a great deal of confusion arose. Three thousand patients suffering from asthma were studied with the hope that skin testing with a vaccine might lead to more conclusive proof regarding bacterial allergy; of these 71.6 per cent showed bacterial reactions, plus other reactions; 21.3 per cent gave only bacterial reactions; 5 per cent gave negative reactions to bacteria, but reacted to other antigens; and 3.1 per cent gave negative reactions to all tests.

Next, we studied the skin reactions to bacteria in those patients with histories of colds and others without such histories. They showed similar types of reactions. In other words, whether the individual had a history of upper respiratory infections or not made no difference. This would lead us to believe that the history of upper respiratory infections was not at all consistent with the reactions.

Next, we classified the size of the reaction according to the age of the individual. At one year the bacterial tests were almost always negative, but the older the individual the larger the size of the reaction until the age of forty. At that age (and older) the reactions seemed about the same. One might conclude from this that the older the patient, the more infections he has had and the more likely that he will show a tuberculin-type reaction to bacteria.

The skin tests to bacterial proteins cannot, therefore, be used as criteria for a diagnosis of bacterial asthma. Then of what value is the skin test to vaccine? If it is of value only in the matter of dosage, those who show a very marked reaction should have well-diluted vaccine and those who have lesser reactions require greater doses. But the diagnosis of bacterial

allergy should not be made by skin test. It should be made entirely from examination and the clinical history. If a patient gives a history of repeated upper respiratory infections followed by asthma, the allergist is justified in concluding that the infection is a primary or trigger factor.

Are we justified in treating cases of asthma with vaccine when there is a history of infection in the patients? This can only be determined by clinical observation. Figures are very confusing and depend upon the enthusiasm of the investigator. The only way a conclusion can be reached in the value of vaccine in the treatment of asthma is by long clinical experience.

In my own experience with 3,602 cases studied, 2,520 were treated with a stock vaccine plus other antigens (70 per cent). Nine hundred twenty-nine cases were treated with stock vaccine, alone, (26 per cent). One hundred fifty-three were treated with autogenous vaccine (4 per cent). Those treated with vaccine and other antigens undoubtedly produced the best results. Those treated with stock vaccine (alone) were 50 to 75 per cent improved. Those treated with autogenous vaccine alone showed about the same relief. This type of evidence is of questionable significance in the absence of double-blind placebo control comparisons, especially in a disease as variable as asthma. We can only estimate their value from the patients' own statements. We must also take into consideration the medications supplementing the treatment and the patients' states of mind.

The debate as to the importance of vaccine therapy will continue. There is a divergence of opinion among men in authority, and until we know the mechanism of the allergic response, or have more reliable tests, we must depend upon our clinical judgment and experience.

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ELIXOPHYLLIN® IN THE TREATMENT OF ACUTE AND CHRONIC ASTHMA: CLINICAL EVALUATION AND PULMONARY FUNCTION STUDIES

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THEOPHYLLINE and its compounds number among their pharmacologic effects the ability to relax bronchospasm, a feature which makes them of great value in the treatment of asthma. In acute attacks aminophylline (theophylline-ethylenediamine) administered intravenously is almost always effective in relieving severe dyspnea. In chronic asthma oral theophylline and its compounds are regularly used to decrease bronchospasm and improve lung function.

The blood theophylline level necessary to relax bronchospasm is approximately 6 mcg/ml, which is the average value reported by Waxler and Schack[6] to follow the intravenous administration of 250 mg of aminophylline. After oral administration of a 200 mg aminophylline tablet the blood level was found to be only about 2 mcg/ml in a half hour. Theophylline and its salts taken by mouth in the usual form are of little value in the treatment of acute asthma because of slow absorption and consequent low blood levels. Attempts to increase the amount taken orally much beyond 350 mg at a time usually result in gastric irritation, without improving the patient's condition.

Schluger, McGinn and Hennessy[4] have shown that the rate and amount of absorption of theophylline from the gastrointestinal tract can be increased greatly by using an alcohol-water solution. This preparation (Elixophyllin, Sherman Laboratories) contains in each 15 cc (1 tablespoon or ½ ounce) 80 mg of theophylline, 3 cc of ethyl alcohol, and flavoring agents. The theophylline content of each 15 cc is equivalent to that of 100 mg of aminophylline. Following the oral administration of 75 cc of Elixophyllin (400 mg theophylline) blood theophylline levels reached a mean value of 8.0 mcg/ml in fifteen minutes, 10.3 mcg/ml in thirty minutes, and 11.0 mcg/ml in sixty minutes. By way of contrast, 500 mg of aminophylline given as uncoated tablets produced theophylline blood values of 1.1 mcg/ml, 3.8 mcg/ml and 7.2 mcg/ml for the same time intervals.[4] The values after Elixophyllin from fifteen minutes on were in excess of the blood levels following the intravenous administration of 250 mg of aminophylline.[6] Elixophyllin should therefore be an acceptable re-

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placement for aminophylline in the treatment of asthma, with the added advantage of substitution of oral for intravenous medication in a certain number of individuals.

The study reported here consists of two parts. The first measured the effect of a single oral dose (or two closely successive doses) of Elixophyllin on patients suffering from acute asthma. The second measured the effect on patients with chronic asthma, who took Elixophyllin at regular intervals each day for many weeks. In both parts of the study a placebo was used for a control period.

PART I. ACUTE ASTHMA

Materials and Methods.—Thirty-five patients who ranged from thirteen to seventy-four years of age, and who came either to the Los Angeles County General Hospital or to the physician's office co-operated in this part of the study. Patients who were in severe status asthmaticus with dehydration, with obvious signs of infection, or who had been given aminophylline within two hours, were excluded.

As soon as the patient had been examined and found acceptable for the study, tracings were made of the 3-second vital capacity (TVC) and the 15-second maximal breathing capacity (MBC), using either a Stead-Wells, or Collins 13-liter Recording Respirometer. Each patient was then given either Elixophyllin or a placebo. Men were given 75 cc; women and adolescents received 60 cc. The placebo used was flavored to resemble the base of Elixophyllin, and contained 3.5 mg quinine hydrochloride per 15 cc, to equal the bitter taste of theophylline. The amount of quinine was only a small fraction of the least medicinal dose. The placebo in this part of the study also contained 20 per cent ethyl alcohol.

The original protocol called for alternate cases throughout the study to be given placebo first. If the patient's condition did not improve on placebo within one half hour, he was to be given an equal dose of Elixophyllin. This procedure was changed after ten cases, because none of the placebo patients got any better within a half hour, and many got much worse. As far as could be determined, neither the alcohol nor psycho-suggestion caused any improvement. Furthermore, when 75 cc of Elixophyllin was given thirty minutes after 75 cc of the placebo, the patients tended to become confused, emotional, somnolent, and difficult to manage.

Pulmonary function readings were taken fifteen minutes, thirty minutes, one hour, two hours (and in some cases three to six hours) after the single dose of Elixophyllin, and at fifteen and thirty minutes after the placebo. Several days later, when the patient had returned to his usual condition, another set of readings was taken.

The readings for TVC and MBC were converted to "per cent of expected normal" for each patient, using the following formulae.

Vital Capacity (West[7])
(Men) Body Surface Area in M^2 x 2.4
(Women) Body Surface Area in M^2 x 2.0
Maximal Breathing Capacity (Motley[2])
(Men) (96—age/2) x BSA in M^2
(Women) (83—age/2) x BSA in M^2
For children and adolescents, these figures were reduced by a factor of .82, as suggested by Pratt and Bushnell.[3]

In a few cases, patients were given successive amounts of Elixophyllin an hour apart, to see whether multiple doses are better than single. More work will need to be done on this technique before any useful conclusions can be drawn.

The first group consisted of fifteen male and twenty female patients. All had moderately severe to severe asthma, from which each had suffered for two years or more. The age distribution is given in Table I.

TABLE I. AGE GROUPING OF PATIENTS WITH ACUTE ASTHMA

Decade	Number
0- 9	0
10-19	4
20-29	1
30-39	6
40-49	9
50-59	10
60-69	3
70-79	2

Results.—Only two patients failed to get some relief from Elixophyllin. Both had severe intrinsic asthma and it was necessary to put both on adrenal steroid hormones after a short hospital stay.

TABLE II. RELIEF OF ACUTE ASTHMA IN THIRTY-FIVE PATIENTS TREATED WITH ELIXOPHYLLIN AND PLACEBO

Degree of Relief†	Elixophyllin		Placebo	
	No. Cases	Per Cent	No. Cases	Per Cent
Complete	2	5.7	—	
Marked	11	31.5	—	
Moderate	12	34.3	—	
Slight	8	22.8	—	
None	2	5.7	10	100*

*Only 10 cases on Placebo.
†Criteria given in text.

Two patients got excellent relief—their asthma was gone in one hour. Eleven patients were classified as obtaining good relief, in that they were able to walk out without further treatment, although still wheezing slightly. Twelve were classified as obtaining moderate relief—these patients were relieved of their "air hunger," but required epinephrine and continued to cough and wheeze slightly. Eight cases were classified as experi-

encing slight relief only. These patients felt a little better, were no longer apprehensive, and after epinephrine were able to leave with extra medication to take home. There was a measurable, though small increase in their pulmonary function. Results in terms of relief are given in Table II.

The average values for T.V.C. and M.B.C. at intervals up to two hours after Elixophyllin are given in Table III.

TABLE III. TIMED VITAL CAPACITY AND MAXIMAL BREATHING CAPACITY AS PER CENT OF PREDICTED NORMAL IN THIRTY-FIVE CASES OF ACUTE ASTHMA TREATED WITH ELIXOPHYLLIN: AVERAGE VALUES

Time	3 Sec. V.C.	M.B.C.
0	37.7%	29.5%
15 min.	41.3%	32.0%
30 min.	47.0%	35.8%
1 hr.	50.4%	38.4%
2 hr.	47.1%	35.5%
After recovery	64.4%	55.5%

On the average, improvement was noticeable within fifteen minutes, and reached its peak at approximately one hour. Subsequently, the average improvement declined, although not all cases gave lower readings at two hours than one hour.

Furthermore, ten cases (29 per cent) showed poorer function at fifteen minutes after Elixophyllin than before taking it, and five (14 per cent) were still slightly below initial reading at thirty minutes. All these cases responded by one hour. Differences in rate of absorption may account for the slow response. But it could also be explained by assuming that factors other than bronchospasm are causing part of the obstruction to air flow.

The per cent of change of the T.V.C. and M.B.C. after Elixophyllin is given in Table IV.

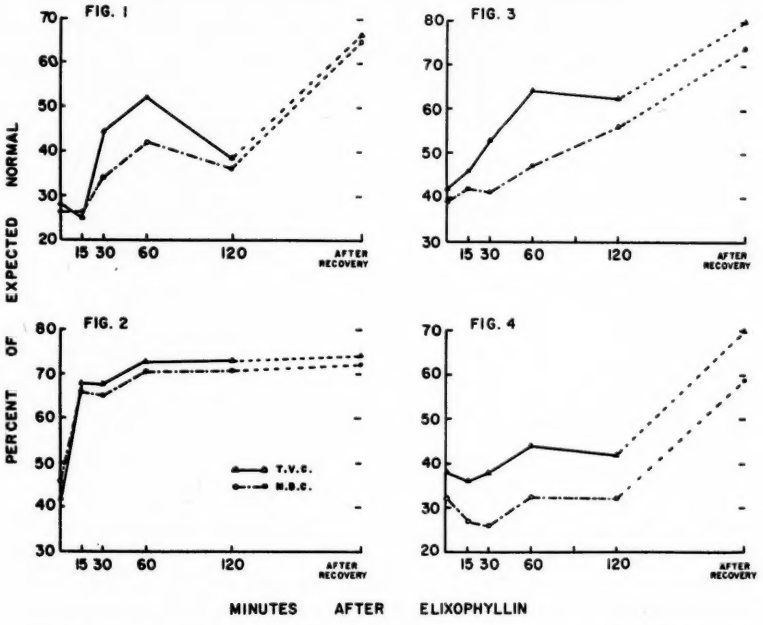
TABLE IV. CHANGE FROM INITIAL VALUES OF TIMED VITAL CAPACITY AND MAXIMAL BREATHING CAPACITY IN CASES OF ACUTE ASTHMA

Treatment	Timed Vital Capacity	Maximal Breathing Capacity
Placebo	15 min.— 0.5%	— 4.5%
10 cases	30 min.—10.1%	— 8.5%
Elixophyllin	15 min.+ 9.6%	+ 8.5%
31 cases	30 min.+24.6%	+21.4%
	1 hr.+33.8%	+30.2%
	2 hr.+25.0%	+20.4%

These values (for T.V.C.) compared well with the improvement after Elixophyllin found by Spielman.[5] In his series of twenty patients with acute asthma, vital capacity increased 39 per cent.

A selection of representative curves of lung function at intervals after

Elixophyllin administration is given in Figures 1 through 3. Figure 1 shows T.V.C. and M.B.C. for a thirteen-year-old boy having severe asthma, whose initial values were less than 30 per cent of predicted normal. These had not improved in fifteen minutes, but then rose rapidly



Figs. 1 to 4. Pulmonary function curves in acute asthma after oral treatment with Elixophyllin. *Solid lines:* 3-second timed vital capacity. *Broken lines:* maximum breathing capacity. See text for description of cases.

and reached a peak at approximately one hour. At two hours, the values had declined slightly, but the patient was not uncomfortable. Several days later, when the attack was well over, his readings were between 65 per cent and 67 per cent of predicted normal.

The curves in Figure 2 show the changes in T.V.C. and M.B.C. that followed administration of 60 cc of Elixophyllin to a woman forty-eight years old. Her initial values were below 50 per cent of predicted normal, but these rose within fifteen minutes to around 70 per cent, where they stayed. Her readings after recovery were not much higher.

Figure 3 shows the curves on a sixty-two-year-old man after 75 cc of Elixophyllin. Initially around 40 per cent, his T.V.C. rose to 64 per cent in one hour and his M.B.C. after a slow start rose to 56 per cent in two hours. His recovery values were between 70 per cent and 80 per cent of predicted normal.

Figure 4 shows the response of a forty-year-old woman after 60 cc of Elixophyllin. Her initial values were between 30 per cent and 40 per cent of normal, and they changed very little in the two hours after treatment.

In Figure 5 are plotted the average values for all thirty-five cases. For

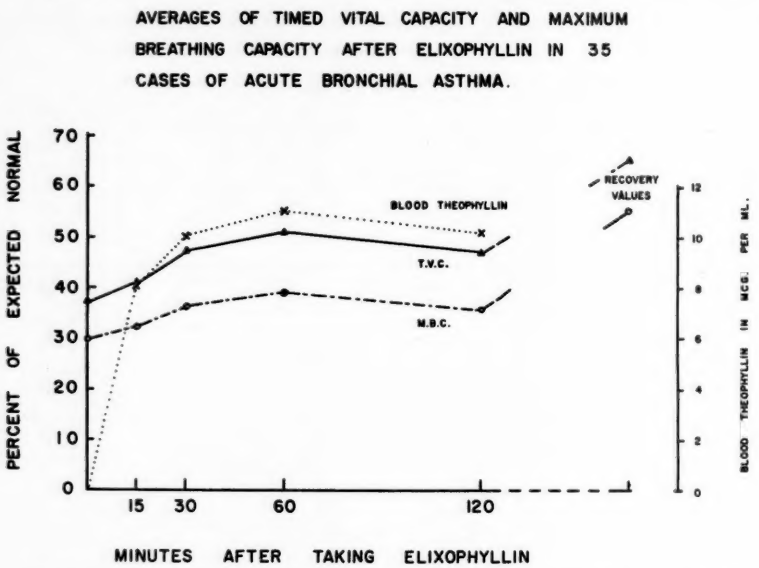


Fig. 5. *Solid line:* 3-second timed vital capacity. *Broken line:* Maximum breathing capacity. *Dotted line:* Blood theophylline levels taken from Schluger, McGinn and Hennessy.

comparison, the curve of blood theophylline after 75 cc of Elixophyllin, as determined by Schluger, McGinn and Hennessy,[4] has been included in the graph. The parallel between the blood theophylline level and the change in average lung function is striking.

The most prominent complaint about Elixophyllin in the acute cases was a burning sensation in the stomach with or without some nausea. Nine (about 25 per cent) of the patients mentioned this. Only one patient actually vomited, and was excluded from this series. Feeling lightheaded or dizzy was a frequent but minor complaint, found only among the women patients. There were two women who went through a weeping spell shortly after taking 60 cc of Elixophyllin, but soon calmed down.

The data presented in this section suggest that on the average Elixophyllin relieves bronchospasm and increases pulmonary function in patients who are having acute exacerbations of their asthma. After a single dose of 75 cc, improvement was noted on the average within fifteen minutes, continued up to one hour, then tended to decline.

Nearly all of the patients studied had some decrease in lung function

continuously present between attacks. Since single doses of Elixophyllin usually did not raise lung function to the resting level and tended to lose their effectiveness after two hours, repeating the dose is probably desirable to get maximum benefit. As individuals vary widely, the need for

TABLE V. CHARACTERISTICS OF GROUP OF CHRONIC ASTHMA PATIENTS TAKING ELIXOPHYLLIN AND PLACEBO

Age Groups	No. Patients	Sex
0- 9 yrs.	0	M-14
10-19 yrs.	3	F-16
20-29 yrs.	1	
30-39 yrs.	5	
40-49 yrs.	5	
50-59 yrs.	10	
60-69 yrs.	4	
70-79 yrs.	2	

Median age—50 years.
Average duration of asthma—7 years.
Severity of asthma:
Moderate (3+) — 7
Severe (4+) —23

extra Elixophyllin should be judged by the patient's response. Allowance should also be made for the fact that about one third of patients do not respond in the first fifteen minutes after taking Elixophyllin.

PART II. CHRONIC CASES

Materials and Methods.—Thirty-six cases suffering from chronic asthma were selected from clinic and private patients to take Elixophyllin and a placebo for three to four weeks each. Six patients were unable to complete the study because of side effects from the Elixophyllin. These cases are discussed below.

The characteristics of the thirty patients who completed the study are given in Table V.

The youngest patient was eleven years, the oldest seventy-four. All patients had had asthma for a minimum of one year; many were lifelong asthmatics. The severity of the asthma was judged as moderate (3+) when symptoms prevented the patient from working, and required daily medication. The asthma was judged severe (4+) when the patient required frequent trips to the hospital for emergency treatment.

To establish a base for comparison, all patients were urged not to use theophylline compounds for one or two weeks, but to control symptoms with epinephrine, isopropylnorepinephrine, propadrine, pseudoephedrine, ephedrine with phenobarbital and potassium iodide.

The dose of both Elixophyllin and placebo was 60 cc (4 tablespoons) four times a day for adult males, and 45 cc (3 tablespoons) for women and adolescents. These amounts were often decreased slightly by the patients themselves depending on the amount of relief experienced.

The placebo used in this part of the study contained 3.5 mg of quinine

per 15 cc. At first 10 per cent to 12 per cent alcohol was added, but patients did not remark on any difference when the alcohol was omitted, so that during the latter half of the study the placebo contained only the bittering agent.

TABLE VI. AVERAGE VALUE OF TIMED VITAL CAPACITY, MAXIMUM BREATHING CAPACITY, SYMPTOM INDEX AND DEGREE OF RELIEF AMONG THIRTY CHRONIC ASTHMATICS BEFORE AND DURING TREATMENT WITH ELIXOPHYLLIN AND PLACEBO

	Initial Value	Elixophyllin	Placebo
Timed vital capacity (per cent of normal)	49.7%	58.5%	49.9%
Maximum breathing capacity (per cent of normal)	35.6%	42.9%	33.5%
Symptom index (Weekly average)		19.5	22.7
Degree of relief* (Weekly average)		2.38	1.08

*No relief—0 Complete relief—4.

Each patient kept a daily record of asthmatic attacks, coughing spells, supplemental medication and an estimate of over-all improvement in symptoms or lack of it. After a short period of trial, patients are able to keep records that have proven more reliable than memory. These data were checked each week and the number of attacks of asthma and/or coughing per week was designated the Symptom Index. The degree of relief was rated from none (0) to complete (4). Thus complete control of asthma for a week would yield a Symptom Index of zero, and a Degree of Relief of 4.0.[1]

During the control period, and once a week during the treatment period, each patient was checked for T.V.C. and M.B.C. as in the first part of this study. The measurements were taken at mid-morning, after the patient had been sitting quietly for one half hour. Readings were taken with the patient standing. The values obtained were converted to per cent of expected normal in each case, using the formulae given in Part I.

Results.—As shown in Table VI, lung function improved modestly in the group as a whole during the time Elixophyllin was being taken regularly. The average value for T.V.C. before treatment was 49.7 per cent of normal; during the month on Elixophyllin this rose to 58.5 per cent, an increase of about 15 per cent. The placebo caused no change on the average from the initial value.

The other function measured, M.B.C., rose from 35.6 per cent to 42.9 per cent of predicted normal during the use of Elixophyllin. This function was more depressed initially than the T.V.C. and the absolute rise with treatment was small. As a percentage of the original value it was 20 per

cent. Again the placebo produced no change from the initial reading on the average.

The Symptom Index, which is primarily a measure of the frequency of asthmatic attacks, showed only a slight decrease with Elixophyllin.

TABLE VII. SUBJECTIVE RELIEF OF CHRONIC ASTHMA IN THIRTY PATIENTS TREATED WITH ELIXOPHYLLIN AND PLACEBO

Relief	Elixophyllin		Placebo	
	Number	Per Cent	Number	Per Cent
Complete	1	3%	0	0
Marked	5	16%	0	0
Moderate	12	40%	1	3
Slight	8	28%	1	3
None	4	13%	0	0

The difference in the Degree of Relief Index, however, was large; it was twice as much on Elixophyllin as on placebo. This was born out by typical comments from patients, such as: "much lighter attacks; can bring up mucus; easier to stop attacks;" et cetera. This would indicate that Elixophyllin used on a regular schedule decreased the severity of asthma in this group, without altering the basic pattern of the attacks.

The subjective relief of asthma experienced individually by the patients on Elixophyllin and placebo is detailed in Table VII.

About 59 per cent of the patients noted a substantial degree of benefit from Elixophyllin, although only one was completely relieved.

It was somewhat unexpected to find such a low incidence of relief (6 per cent) from a placebo, which can usually be counted on to cause "improvement" in about one subject in eight. It may be that in patients with chronic intrinsic asthma of this type, suggestion has very little influence compared to organic factors.

The outstanding complaint regarding Elixophyllin was nausea and gastric irritation. This was most pronounced when the solution was taken on an empty stomach, and varied with the amount taken. Six adult patients originally scheduled for this study were unable to continue; five because of nausea with or without cramps and diarrhea, or nausea and increase in asthma, and one because of increase in bronchospasm with each dose of Elixophyllin.

The side effects encountered are listed in Table VIII. On the full initial dose of Elixophyllin, a total of ten patients complained of some degree of gastric disturbance (an incidence of 33.3 per cent), but they were willing to continue because of the effect on their asthma. Gastric distress became less of a problem if Elixophyllin was taken when some food was present in the stomach, and as the dose was decreased after the test period.

An itching erythematous rash on the neck, back, chest and upper arms appeared in one patient during the third week on Elixophyllin. This rash

cleared when Elixophyllin was replaced by the placebo, and reappeared when the medication was tried again.

The placebo caused nausea in one patient and an increase in asthma in another.

TABLE VIII. SIDE EFFECTS COMPLAINED OF BY THIRTY ASTHMATIC PATIENTS ON ELIXOPHYLLIN AND PLACEBO

Side Effect	Elixophyllin Number of Cases	Placebo Number of Cases
Nausea		
Mild	3	0
Moderate	4	1
Severe	2	0
Vomiting	2	0
Cramps	1	0
Diarrhea	1	0
Insomnia	1	0
Headache	1	0
Rash	1	0
Asthma	0	1

DISCUSSION

In severe acute asthma not responsive to epinephrine, theophylline preparations may be the only recourse. Because of slow absorption and gastric irritation when taken orally, theophylline-ethylenediamine is effective in acute attacks only when given by vein. As this calls for special equipment and skill, any method that promises to substitute oral medication is well worth considering.

The study presented here indicates that a hydro-alcoholic solution of theophylline when taken by mouth in adequate doses produces an increase in pulmonary function in asthma. In acute attacks, the effect is noticable on the average in fifteen minutes, and increases for one hour. Not all cases respond this rapidly, indicating that there may be different rates of absorption, or that factors other than bronchospasm are important. Those patients who do respond well to Elixophyllin, and they amounted to 19 per cent of the acute cases, may be spared the inconvenience of intravenous aminophylline in many of their attacks, and can assume more responsibility for their own treatment. Those who do not respond readily will require intravenous aminophylline or hospital treatment.

Spielman[5] in reporting on twenty cases of acute asthma found that all of them noted good to excellent relief of symptoms after 75 cc of Elixophyllin. In our series of thirty-five cases of acute asthma, ten (27.5 per cent) obtained practically no relief. The difference may be explained by the fact that his patients had less initial depression of lung function, and were better able to respond to the bronchodilator.

In chronic asthma, the routine use of Elixophyllin decreases the severity of bronchospasm, in line with its theophylline content, but does not alter the basic pattern of the disease except in a very few cases. In this respect it has the same effect as other forms of theophylline. Gastric distress

with continuous use was complained of by a third of the patients, but this tended to disappear when the dose was reduced or if taken along with some food.

Elixophyllin appears from this study to be a useful preparation for the control of bronchospasm in asthma. As with other methods of treatment, its use must be adjusted to the individual patient's needs, as dictated by experience and clinical judgment.

SUMMARY

1. A solution containing 80 mg theophylline and 3 cc of ethyl alcohol per 15 cc was given by mouth to thirty-five patients with acute asthma, and thirty patients with chronic asthma.

2. In the acute cases, 3-second Vital Capacity increased by 33.8 per cent and Maximal Breathing Capacity by 30.2 per cent one hour after 60 to 75 cc of the theophylline solution was administered.

3. On a placebo solution, both measures of lung function declined during the first half hour.

4. Seventy-one and a half per cent of the patients having acute asthma felt moderate to complete relief of symptoms.

5. In chronic asthmatics, the regular use of the theophylline solution did not alter the frequency of asthma in most cases, but decreased the severity in 59 per cent.

6. Gastric irritation was the main side effect complained of by 33.3 per cent of the patients with chronic asthma and 25 per cent of those with acute asthma. This could be reduced by appropriate measures.

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TRUTH OF SCIENCE

The Truth of Science has ever had not merely the task of evolving herself from the dull and uniform mist of ignorance, but also that of repressing and dissolving the phantoms of the imagination.—MICHAEL FARADAY.

THE USE OF TRIAMCINOLONE IN THE TREATMENT OF ALLERGIC DISORDERS

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THE ACTION of adrenocorticosteroids in allergic diseases is essentially one of controlling serious or distressing symptoms of a limited acute reaction or an acute exacerbation of a chronic process. The ability of these agents to decrease tissue permeability, markedly to diminish or even to abolish perivascular exudation and edema formation, and to suppress successfully an acute inflammatory situation has firmly established their usefulness in the management of hypersensitivity reactions. Some degree of clinical improvement is almost always obtained from them and, not infrequently, all objective and subjective evidence of active disturbance may subside within hours to a few days after initiation of treatment. An allergic reaction may be contained pending definition and thorough diagnosis and the institution of specific hypo-sensitization measures if these things are possible. A self-limited disease may be speedily terminated or repeated flare-ups of long-standing disease may be treated as they arise since subsequent courses of corticoid therapy are as effective as the original. This class of compounds and particularly the newer agents offer symptomatic relief welcomed by the patient and not previously available with conventional therapeutic tools.

Triamcinolone possesses in common with other steroids the anti-allergic, anti-inflammatory and anti-pruritic properties useful in the management of allergic disease. It has proved somewhat more potent than either prednisone or prednisolone on a weight basis[1-5] and less disturbing where salt retention and edema are critical factors. In fact, the mild diuretic activity of the compound[5-7] is highly desirable and makes it preferable to older corticosteroids. A number of favorable experiences attest to the effectiveness of triamcinolone in the management of allergic diseases[1,3,5] and various cutaneous eruptions.[2,4,8-10] The compound appears particularly valuable in dermatology and, in relatively small doses, exerts an unusual and what seems to be a virtually unique suppressive effect on psoriasis.[8,10]

The patient group given triamcinolone during this investigation for relief of either cutaneous or respiratory manifestations of hypersensitivity was considered representative of allergic practice with regard to age, sex and spectrum of presenting complaints. Selection was based on an obvious need for prompt relief of a severe and distressing symptomatology, diagnosis of a corticosteroid-responsive disorder and, in most cases, refractoriness to antihistamines or broncho-dilators. Follow-up for adequate evaluation of clinical response was possible in all cases reported in this series.

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MATERIALS AND METHODS

A total of 109 children and adults with allergic disease, seventy-five with respiratory symptoms and thirty-four with dermatoses, were treated with triamcinolone.* The distribution of cases is given in Tables I and II. Both male and female patients ranging in age from six months to seventy-five years were given the oral

TABLE I. CLINICAL EXPERIENCE WITH KENACORT—TREATMENT AND RESPONSE OF RESPIRATORY DISORDERS

Disorder	No. of Patients	Period of Treatment (days)	Dosage (mg.)		Response to Treatment			
			Initial	Maintenance	Excellent	Good	Fair	Poor
Bronchial asthma	32	2-65	6-24	0.5-8	29	2	1	0
Hay fever	19	2-54	4-16	2-12	16	0	3	0
Asthma and hay fever	17	1-38	4-16	1-4	12	3	1	1
Emphysema	1	16	24	8-16	1	0	0	0
Emphysema and pulmonary fibrosis	1	20	24	16	1	0	0	0
Bronchitis and emphysema	1	17	16	8	1	0	0	0
Allergic rhinitis	4	9-33	16	2-8	3	1	0	0
Totals	75				63(84.0%)	6(8.0%)	5(6.7%)	1(1.3%)

steroid in short courses of therapy extending from one to seventy days in duration. With few exceptions, virtually every patient reported unsatisfactory experiences with conventional antihistamine or bronchodilator medication. Pretreatment blood pressure levels and body weight were recorded so that any steroid-induced deviations from the normal could be detected during, and at the completion of, treatment. Because of the prominent subjective component in allergic disease, patients were

TABLE II. CLINICAL EXPERIENCE WITH KENACORT—TREATMENT AND RESPONSE OF DERMATOSES

Dermatoses	No. of Patients	Period of Treatment (days)	Dosage (mg.)		Response to Treatment			
			Initial	Maintenance	Excellent	Good	Fair	Poor
Atopic dermatitis	3	12-42	4-16	1-4	3	0	0	0
Contact dermatitis	7	4-30	16-24	4-8	7	0	0	0
Poison ivy dermatitis	5	4-21	8-24	4-8	5	0	0	0
Urticaria	6	4-31	8-16	4-8	4	0	1	1
Eczema and eczematoid eruptions; other allergic dermatitides	13	7-70	4-16	1-8	12	1	0	0
Totals	34				31(91.2%)	1(2.9%)	1(2.9%)	1(2.9%)

given triamcinolone without being told of the nature of the agent or the results which might be anticipated. Careful questioning during follow-up visits, however, was employed to obtain a subjective as well as objective picture of the overall response to the corticoid.

Dosage.—In general, a priming dose of 16 to 24 mg. of triamcinolone daily was found desirable for adults. The larger dose proved necessary where the patient was

*Triamcinolone was supplied as Kenacort® by E. R. Squibb & Sons, New York, New York.

severely distressed as during an acute asthmatic situation or in case of status asthmaticus. For most individuals, 16 mg. per day was an adequate initial quantity of steroid for prompt control of allergic symptoms. The priming dose was administered for two days or, at most, three days after which dosage was gradually reduced to maintenance levels. Doses of 8 mg. daily were found adequate for maintenance in the majority of cases although with some adults, 4 mg. provided sufficient steroid activity. When dosage was reduced stepwise, a low of 2 to 4 mg. daily could be attained without interruption of steroid benefits.

Children over 60 pounds in body weight required approximately one-third the adult dose for initial termination of the acute attack and a noticeably small maintenance dose of 2 mg. per day to continue clinical benefits. With children under 60 pounds in weight, 1 to 2 mg. per day generally maintained a clinical response.

THERAPEUTIC RESULTS

As may be seen from Table I, of the seventy-five patients with respiratory disorders, sixty-three (84.0 per cent) showed an excellent response to treatment, six (8.0 per cent) a good response, five (6.7 per cent) a fair response, and one (1.3 per cent) a poor response to triamcinolone. In the bronchial asthma group, twenty-nine of thirty-two patients obtained relief of breathing difficulties and improvement in chest symptoms in a matter of hours and it was gratifying to both physician and asthmatic that an acute episode could be so rapidly terminated. Similarly, triamcinolone promptly alleviated respiratory distress in sixteen of nineteen cases of hay fever, twelve of seventeen cases where hay fever symptoms were superimposed upon bronchial asthma, three cases of emphysema and three of four cases of allergic rhinitis. Where the response to triamcinolone was poor, in one instance, elevation of dosage provided the additional steroid stimulus necessary for the desired therapeutic result.

The clinical response to triamcinolone observed in thirty-four patients with allergic and inflammatory skin eruptions is reviewed in Table II. Results of prescribed treatment were excellent in thirty-one cases (91.2 per cent), good in one (2.9 per cent), and fair in one, while one patient with urticaria responded poorly. Dermatologic patients generally required relatively small doses of triamcinolone for clearing of lesions and resolution of disease. In these cases, the initial discomfort was sufficient to warrant a short course of corticosteroid therapy and the results justified the administration of triamcinolone. The dramatic symptomatic relief that is often seen with an effective steroid in amenable dermatoses is unmatched by other forms of treatment favored in pre-steroid practice.

Side Reactions.—Unwanted reactions during short-term therapy with triamcinolone included anorexia, fatiguability, constipation, weakness, flushing erythema of neck areas, vertigo, headache, indigestion and weight loss. Gastrointestinal symptoms were present in one patient who previously experienced such symptoms as a result of peptic ulcers. In no case was special medication required to suppress any side effects induced by the corticoid. During maintenance therapy, averaging several weeks

in some individuals, no change was observed in normal appearance or personality and no weight gain or blood pressure elevation occurred. With relief of allergic symptoms, a sense of well being developed and patients commented spontaneously on their excellent health. No effects on dietary habits or appetite were noted during this investigation although no attempt had been made to impose dietary restrictions. While detailed electrolyte balance studies could not be carried out none of these patients exhibited any electrolyte difficulty which was translated into clinical terms.

OBSERVATIONS

In our experience with the various naturally occurring and synthetic steroid compounds developed during the past ten years, consideration of the general welfare of the allergic patient recommends the use of triamcinolone. Ease of administration, the relatively low dosage required to carry the patient through the severe and disabling episode, the minor nature of most unwanted effects encountered during short courses of anti-allergic therapy, and a high degree of efficiency as a palliative medication are decided advantages in the treatment of allergic disease. Like other corticoids, triamcinolone is not a substitute for sound allergic diagnosis, hyposensitization or control of intrinsic and environmental irritants but, where exacerbations occur despite the best efforts of the allergist, it promptly contains and controls symptoms of hypersensitivity. Triamcinolone also proved useful in hyposensitization programs, averting systemic reactions to progressively higher allergen doses.

During this study, relief of acute symptomatology was often obtained in a matter of hours with priming dosage after which improvement could be maintained with a fraction of initial doses. Medication was withdrawn gradually and in stepwise fashion to avoid symptoms of adrenal insufficiency. No difficulties and no rebound effects were noted with this program. Where triamcinolone was withdrawn in a few days, steroid benefits appeared to persist for approximately ten to fourteen days before a return of disturbing symptoms was observed. With triamcinolone, steroid medication could be employed in the cardiac and in the hypertensive individual and no effects on blood pressure levels occurred in hypertensives treated for allergy. These was no incidence of fluid retention and in one severe cardiac patient, a desirable diuretic effect was seen during treatment.

SUMMARY

In the treatment of cutaneous and respiratory manifestations of allergic disease, triamcinolone proved a highly efficient corticoid prompt in action and well suited to carrying the patient through severe and disabling episodes. Short courses of therapy, indicated in most allergic patients, produced unwanted effects that were minor in nature and required no

special treatment. Of seventy-five patients with respiratory disorders treated during this investigation, sixty-nine (92.0 per cent) showed a good to excellent response. Good to excellent clinical benefits were also achieved in thirty-two of thirty-four (94.1 per cent), of the cases of allergic and inflammatory dermatoses treated with the corticoid. Dosage and side effects are described and observations on the usefulness of the compound are presented.

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NATURE OF RESEARCH

In the long view, progress through research discloses itself as an evolutionary process. We may draw an analogy between the research performed consciously and with intent by man, and unconscious research on the part of nature. As man sets up experiments to find new truth, so does nature, in the case of living organisms at least, make experimental types through the process of mutation, and test them out in the struggle for existence. Thus we believe has the evolution of species come about, and in similar fashion has man acquired new knowledge and learned to improve his ways of approaching his objectives. As does nature, under an irresistible drive to procreate, force life to adapt itself to every environment, no matter how inimical, capable of supporting life at all, so does man under his drive to know, inquire into and explore every region of his cosmos to which his sensibilities and his intelligence direct him. JAMES HOWARD MEANS, "Kober lecture," Georgetown, 1955.

NUMMULAR ECZEMA WITH SPECIAL REFERENCE TO DERMATITIS OF THE HANDS IN HOUSEWIVES

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NUMMULAR eczema, a distinctive eczematous dermatitis, is related neither to contact type of allergy nor to atopy. At first glance this may be surprising since the morphologic and even histologic findings do not differ fundamentally from those of the contact type eczematous dermatitis. Undoubtedly this is one of the reasons why the recognition of nummular eczema as an entity has met with considerable difficulties.[1-6]

The situation has not improved by the recent trend to speak of nummular dermatitis and to use this name as a synonym for a patchy eczematous eruption. There are other types of dermatitis which occur in coin-shaped lesions, but their nosology and response to therapy differ greatly from that of nummular eczema. It might help to clarify these differences if we used the descriptive name discoid dermatitis for this group, and reserved the name nummular eczema for a specific entity. If I need to defend the word eczema I can readily do so by saying that nummular eczema is a disease due to intrinsic factors. The older dermatologists frequently spoke of "true eczema" to set it apart from contact dermatitis and disseminated neurodermatitis.

Although the clinical picture of nummular eczema is fairly typical, the explanation for the coin-shaped character of the lesions and the well-known tendency to reoccur in fixed sites is still lacking.

The size of the lesions varies from that of a dime to palm-size plaques. The distribution and number of patches varies but the dorsums of the hands and the extensor surface of the extremities are the sites of predilection. Less frequently the shoulders, buttocks, face, breasts and nipples are involved. Morphologically speaking, we find two types of manifestations which may be present simultaneously or appear in the course of evolution and involution. Rhagadiform eczema consists—to quote Becker and Obermayer—"of isolated plaques, which are dry, slightly scaly and erythematous, and the surface of which has the appearance of very superficial fissuring.

The vesicular phase of nummular eczema is characterized by fairly well-defined coin-shaped patches. They are erythematous, edematous, and studded with small vesicles, papulovesicular lesions and pin-head size crusts. The degree of edema may vary in different stages of evolution and involution, as does the amount of active vesicles and papules. Exudation fol-

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lowed by formation of discrete crusts is moderate, unless complications develop.

At the stage of involution, the vesicular plaques may show areas of normal skin or the stage of rhagadiform eczema, with a scattering of papules and papulovesicular lesions throughout. Recurrences frequently follow this pattern before they evolve into solid plaques and strikingly take place in the sites previously affected. This may give the impression of a fixed drug eruption, but true dermatitis medicamentosa does not have the morphology of eczematous dermatitis unless sensitization from without to within has occurred.

Three factors may change the clinical picture of nummular eczema.

1. Irritation by soaps and alkalis or by therapeutic applications including drying lotions will produce a Koebner phenomenon by increasing the acuity and/or size of the nummular patch.

2. An intercurrent contact allergy most frequently acquired by topical remedies will masque the features of nummular eczema by giving rise to a diffuse contact type of dermatitis.

3. Pyogenic infection and sensitization to pyogenic organisms will increase the exudation of the nummular lesions, add pustular or vesicopustular elements, impetiginous crusting, and features resembling a dermatitis repens to the typical picture. It is important to recognize this phase of nummular eczema since it is not uncommon, especially on the hands, and calls for the addition of topical or systemic antibiotics.

The clinical examination of the patient is not complete unless the entire skin surface is carefully scrutinized. Dryness of the elbows and knees, xerosis of the ankles and legs, follicular keratosis of the extensor surface of the arms, buttocks and thighs, and occasionally true ichthyosis simplex characterize the patient susceptible to nummular eczema or the housewife suffering from dermatitis of the hands. The age incidence favors adult life and advanced age, suggesting that aging of the skin may be a contributing factor.

On the other hand, an important group of nummular eczema is the one found in infants and young children. It does not differ from the disease of adults except for its wider distribution and frequent involvement of the diaper area and the perioral region of the face. Its recognition and differentiation from the infantile type of atopic dermatitis will detract from allergic tests, elimination diets, et cetera, and focus attention on bathing habits, avoidance of excessive changes in temperature and on supplementation of the diet with Vitamin A, B complex and unsaturated fatty acids.

A history of the patient afflicted with nummular eczema will produce some almost stereotype facts which are as typical as the morphologic fea-

tures. Itching is present in various degrees, especially in the eruptive stage, but usually is not as severe as in atopic dermatitis or acute contact dermatitis. A sensation of burning aggravated by bathing is a frequent complaint. The appearance of lesions with the onset of cold weather in late autumn or early winter and improvement or complete disappearance in summer or warm climate will be promptly asserted by patients who had been victims of annual recurrences. A question regarding chapped hands in the winter long before the first attack of eczema will often be answered in the affirmative. The appearance of nummular eczema or rhagadiform eczema in people coming from subtropical regions (Central and South America) to cold or moderate climate is a frequent observation.

A good dietary history should be obtained and will often reveal poor eating habits, especially a lack of vegetables, salads, and milk. Diseases known to lead to conditioned nutritional deficiencies such as diabetes. hypothyroidism, gallbladder and liver disease, gastric and duodenal ulcer, ulcerative colitis, hypercholesterolemia and others are significant. A period of emotional or physical stress—including acute infections, operations, pregnancy, and difficult childbirth—often precedes the onset of nummular eczema or dermatitis of housewives.[7,8]

DERMATITIS OF THE HANDS IN HOUSEWIVES[7,8]

As pointed out before, the extensor surface of the extremities is a site of predilection of nummular ezcema. The dorsums of the hands are most commonly involved and may be the only areas affected.

If the eruption is solely confined to the hands and the patient's occupation necessitates frequent contact with soap, detergents, alkalis, solvents and other drying agents, we speak of occupational contact dermatitis, primary irritant dermatitis or ezcema of housewives. These designations are acceptable only if we recognize the true nature of the eruption which in many instances represents a form of nummular eczema. Much of the persistence of these cases is due to the fact that exposure to the specific irritants, banal trauma and pyogenic infections are more difficult to avoid, because of the anatomical and functional distinction of the hands. Furthermore, the nature of primary irritant dermatitis is that of a toxic effect on the skin, which explains the persistence of the eczematous dermatitis after the cause has been eliminated. This in itself differentiates between it and the allergic type of contact dermatitis.

More specifically, the dermatitis of the hands in housewives illustrates the mechanism of toxic hypersensitivity, an apparently paradoxical term used by Burckhardt.[9] It means that there are predisposing factors partly of intrinsic nature which bring about the eczematous reaction to alkalis (soaps).

One way of visualizing the functional defect of the skin prone to develop a soap dermatitis is to perform the alkali neutralization test of Burckhardt.[9]

TECHNIQUE OF ALKALI NEUTRALIZATION

The site to be tested on the extensor surface of the forearm or back is marked with a Dermatograph. One drop of a freshly prepared 1/80 n sodium hydroxide solution is applied to it from a pipette. A drop of 1:2000 alcoholic phenolphthalein solution is added and both drops are covered with a glass or lucite bloc, measuring 2 × 3.5 × 1.5 cm. By gentle movements of the bloc the solution is kept in close contact with the skin.

The time necessary to make the pink solution colorless, that is to neutralize down to pH 8.3, is noted. This procedure is repeated ten times at the marked site, cleansing the skin and glass bloc with cotton each time.

The first few measurements usually last a few seconds; and with the later ones, the neutralization time goes up to several minutes. The results are classified as follows: (1) Quick neutralization (none of the ten measurements requires more than five minutes). (2) Intermediate neutralization (one or more of the measurements requires more than five minutes, but not over seven minutes). (3) Slow neutralization (one or more of the measurements requires over seven minutes).

The technique is rather simple but tedious, and if followed meticulously, highly accurate. This can be demonstrated by using a glass electrode and Beckman Potentiometer rather than phenolphthalein as an indicator, marking the time when pH 8.3 is reached.

Burckhardt and others have demonstrated that the majority of patients with cement dermatitis, alkali eczema and dermatitis of housewives show an impaired alkali neutralization. In collaboration with Drs. Chester, Blade and Sloane, I was able to show that dermatitis of housewives not only has the clinical features of nummular eczema and usually occurs in women with xerosis of the skin, but that nummular eczema and dermatitis of housewives are characterized by a poor or at best intermediate alkali neutralization test. This includes the dermatosis of the hands seen in physicians, surgeons, dentists, bartenders, soda fountain clerks, dishwashers and other occupations which necessitate the frequent use of soaps and detergents with a high pH.

The Germans designate these eczemas as "Abnutzungs Dermatosen" a word which could be translated by speaking of dermatoses due to prolonged "wear and tear." "Traumiteratives Eczem" is another term recently introduced by Hagerman.[11]

THE PHYSIOLOGIC BACKGROUND OF ALKALI NEUTRALIZATION

The determination of the pH of the skin has interested dermatologists for many years and the acid reaction of the normal skin was considered rightly as a protective mechanism against alkalis, and, indirectly, against infection with pyogenic organisms and fungi. The use of accurate techniques employing the potentiometer and special skin electrodes has shown

that the variations of the pH of the skin do not give us sufficient information about the behavior of various dermatoses.[8,9]

It is only by using alkali neutralization tests that valuable differences can be demonstrated. Extensive research by Burckhardt and many other authors has clarified the mechanism of alkali and acid neutralization, and shown that it is primarily the function of the amphotheric amino acids of the horny layer. The role which the sweats play in alkali neutralization is minor and based primarily again on the amino acids derived from the horny layer. Only some elaborate studies of the last few years,[12] based on chemical analysis of the horny layers of the epidermis and using the stripping technique have localized the so-called barriere as the functioning portion of the horny layer. The findings of Szakall are so important that I like to quote from his summary:

"The first time in this work freshly formed horny layer from the living epidermis of man was isolated and examined. It represents morphologically a coherent membrane which is located immediately above the stratum granulosum and is designated as barriere, stratum corneum conjunctum. It contains with a remarkable constancy 42 per cent water soluble extractives and 58 per cent structual keratin.

"It was established that the acid reaction of the barriere is due to the partition representing 17.6 per cent and containing amino acids. These amino acids are either free or loosely bound . . . if the amino acids are washed out from the barriere one finds no noticeable H-ion concentration. The ability of neutralizing alkalis and binding acids is also lost to a large degree."

Szakall points out further, that the water soluble extractives are also present in the uppermost part of the horny layer (stratum corneum disjunctum), although in smaller amounts. The acid reaction in this stratum and on the skin surface is less than in the barriere. The difference is due to the cations of the sweats which form salts with the free amino acids. The protective action of the water soluble extractives of the horny layer is not confined to the neutralizing function of the amino acids. According to Szakall, 22 per cent of the extractives are purine derivatives, originating from the nuclei of the keratinizing cells. It could be demonstrated that they play an important role in the protection of the skin against the damaging action of actinic rays on mitosis. Another function of the water soluble extractives, based on their highly hygroscopic quality, is the maintenance of the water content of the horny layer. Without them the barriere is not capable to bind more than a fraction of the water normally present in its cells.

The extensive data offered by Szakall supply ample proof that the water soluble extractives are formed in the process of keratinization. While the insoluble keratin structure primarily takes over the protection against mechanical insults, the water soluble extractives have been assigned to a multiplicity of chemical protective functions.

These facts and figures presented by Szakall, and further broadened in his recent book dealing with the action of soaps and detergents on the

skin, makes it clear that the structural and functional integrity of the horny layer is dependent on a normal cellular metabolism of the skin. Disturbance of enzymatic processes concerned with normal keratinization by disease, nutritional insufficiency or acute and chronic stress (transmitted by a neuro-vascular mechanism to the skin) will impair this defense of the skin against chemical and physical injury.

The earliest signs of this metabolic insufficiency of the skin leading to impaired alkali neutralization and waterbinding ability of the skin are xerosis and chapping. Clinical experience has taught us that in addition to the wear and tear caused by primary irritants, climatic, constitutional and emotional factors are part of the pathologic constellation which leads to the eczematous reaction known as Nummular Eczema.

DIFFERENTIAL DIAGNOSIS[13]

There is no doubt that much will have to be added to our knowledge before we can fully understand the etiology of nummular eczema. Nevertheless, the sum total of anamnestic, clinical and laboratory data is sufficient to establish nummular eczema of the disseminated and localized type as a clinical entity.

In the large group of cases of eczema of the hands, nummular eczema and dermatitis of housewives play a dominant role. It is an erroneous simplification to speak of contact dermatitis whenever there is an involvement of the hands with an eczematous type of dermatitis. While a careful history and patch testing should not be omitted, a contact allergic type of dermatitis will offer certain characteristic features which differ from those of the nummular eczema group.

With the exception of some peculiar localizations due to certain occupational contactants, allergic contact dermatitis is a more diffuse process, involving the dorsums of the hands and frequently the flexor surface of the wrists. In more severe cases, chemical id reactions or spreading by continuity to the antecubital fossae and to the face takes place, often associated with swelling of the eyelids.

Atopic dermatitis frequently involves the dorsal aspects of the wrists and sometimes the dorsums of the hands. A typical history and other lesions of flexural neurodermatitis and the predominance of lichenification will simplify the diagnosis. A more difficult problem is the etiologic diagnosis of eczema of the hands due to food allergy, if there is a lack of atopic history and a patchy and vesicular form of neurodermatitis present. The careful studies by Rowe, Flood and Perry,[14] Winston and Sutton[15] and Pillsbury and Livingwood[16] leave no doubt that food allergy may in some instances cause a persistent eczema of the hands, but such cases represent a small minority in the large group of eruptions of the hands.

Discoid eczematous plaques of the extremities are part of the distinctive dermatosis originally described by Sulzberger and Garbe.[17] They involve the flexor surfaces and extensors of the extremities and are more exudative

than lesions of nummular eczema. Involvement of the nose, perioral region, glans penis, combination with lichenoid and lichenified plaques on the trunk, unbearable pruritus and unequivocal eosinophilia in the blood are only a few of the features which should lead to the diagnosis of this comparatively rare but important dermatosis.

An eczematous variant of dermatitis herpetiformis of Duhring has been described by Gordon and Lowenthal,[18] but widespread nummular eczema should not be considered as a form of Duhring's Disease and treatment with sulfonamide drugs[19] may have an unfavorable effect. Pillsbury *et al*[20] have classified autosensitization dermatitis as a form of nummular dermatitis. That may be so, but the presence of a chronic, infectious eczematous dermatitis (frequently seen in a varicose complex) or the presence of a chronic focus of infection is essential for the diagnosis of autosensitization dermatitis.

The sudden onset of this complication frequently triggered by a sensitizing topical application to the primary focus of infectious eczema, regression after systemic antibiotic agents and a short course of steroid therapy leave no doubt that this condition bears no relationship to nummular eczema.

Many dermatoses may assume an atypical appearance when they are confined to the hands, and psoriasis, lichen planus and lichen simplex chronicus of the hands thus may be mistaken for nummular eczema.

It is a peculiarity of nummular eczema to form dysidrotic vesicles[21] in lesions which have extended to the lateral and volar surface of the fingers and occasionally to the palms. In such cases a diagnosis of dysidrotic eczema or dermatophytid may be entertained mistakenly. The coin shape of nummular eczema, the occasional tendency to central healing and, of course, the distinctly vesicular morphology are responsible for the old synonym of trichophytosis-like eczema. This may explain why the suffering of patients with nummular eczema is frequently aggravated by antimycotic therapy based on a diagnosis of fungus infection. Primary dermatophytosis of the palms is not common, is usually unilateral, and involvement of the dorsums of the hands is a rare occurrence.

THERAPY

Treatment of nummular eczema should take cognizance of the features which are the common denominators of the disease and of other factors which may be presented by the individual patient. The first objective should be to clear up the eczematous dermatitis. This can be accomplished if soaps, detergents, alkalis and other irritants are strictly avoided in bathing, washing the hands or working in the kitchen. It can be facilitated by giving instructions about the use of a colloidal bath, using either cooked oatmeal, Aveeno or Soyaloid for the bath. Aveeno and Soy-Dome cleansers are free of soaps and detergents and can be used for washing the hands.

Topical therapy can best be carried out with a Hydrocortisone cream. It is of distinct advantage to use an oil in water emulsion base with a

low pH for every medication prescribed for nummular eczema and dermatitis of housewives.[8,22]

If there is evidence of pyogenic infection, a broad-spectrum antibiotic agent should be used locally, and, if necessary, systemically. After the infectious phase has subsided a combination of hydrocortisone with a broad spectrum antibiotic agent or iodochlorohydroxyquinoline should be used for after treatment. When the eczematous dermatitis has receded and residual dry lesions are present, frequent lubrication with an acidifying cream should be carried out during the day and applications of hydrocortisone cream continued at bedtime.

If there are resistant eczematous patches which are not due to secondary infection the addition of coal tar to the hydrocortisone cream is frequently useful, and at times coal tar paste prepared after White's formula may be more effective than the newer preparations. If coal tar is not well tolerated, bituminous tars like Ichthyol or Tumenol can be used.

The question as to whether topical steroid therapy is superior to the older remedies, especially tar, has to be settled in the individual case. As a rule, the patient prefers the clean and simple application of a colorless, odorless and non-greasy cream to the tar ointment. This is true not only in patients with nummular eczema, and in particular housewives preoccupied with their hands, but also for people suffering from atopic dermatitis, contact dermatitis, circumscribed neurodermatitis, pruritus vulvae, ani, et cetera. Recurrences of nummular eczema are frequent, especially in the wintertime and when the patient, encouraged by improvement, becomes careless about avoidance of soaps and detergents or is forced by his occupation to use them. Therefore, active therapy should be continued after complete healing and the patient should be appraised of the need of gradually weaning his skin back to normal function.

This brings us to the long-range objective of correcting the metabolic defects of the skin, which predispose to alkali sensitivity and nummular eczema. It necessitates a search for the causes of dry skin. While there are constitutional and at times hereditary factors which are responsible for this abnormality definite improvement can be obtained by nutritional therapy.[5,23]

Since we have seen that alkali neutralization is dependent on the free amino acids of the stratum conjunctum of the horny layer, normal keratinization is one of the objectives of therapy. Vitamin A therapy seems to be justified[5,24] providing one keeps in mind that prolonged, periodic administration of therapeutic but not excessive doses is necessary, to correct a disturbance in absorption and utilization of this vitamin. The synergistic action of ascorbic acid, riboflavin, Vitamin E, lipotropic substances like soybean phosphatids and essential unsaturated fatty acids should be utilized to help improve Vitamin A metabolism.

Hypothyroidism, gallbladder disease, disturbances of liver function and diabetes, if present, will make the task even more difficult.

The local care of the dry skin is important for the prevention of nummular eczema and dermatitis of housewives.

After the attack of dermatitis has subsided, the patient should be conscious of the fact that excessive use of soap, hurried and improper drying after bathing and washing, overheating of living and working quarters, excessive sunbathing and the use of drying lotions and powders are to be avoided at all times.

The use of lubricating creams is to be encouraged well before the onset of the critical seasonal changes of weather.

The choice of the lubricating cream should not depend only on its "moisturinizing" properties, but mainly on the low pH of the cream.

This is also true for the so-called protective creams which in the active stage of soap and detergent dermatitis are irritating, and to be effective as prophylactic agents, should be able to neutralize alkalis. Dependence on the protection of the hands by rubber gloves only should be discouraged, since it is not complete and the prolonged use may add undesirable irritation due to decomposition of sweats.

Even a condensed discussion of therapy of nummular eczema and dermatitis of housewives would not be complete unless consideration is given to the psychosomatic implications of the disease.

To accept the role which psychogenic impulses play in inflammatory diseases of the skin is not in contradiction to the concepts of a metabolic insufficiency of the skin and the impairment of its protective functions. A parallel can be found in other known diseases of metabolism, for instance diabetes and hyperthyroidism. Certainly it does not justify a concept of nummular eczema as an "acute neurodermatitis," just as its susceptibility to pyogenic infection does not permit its interpretation as infectious eczematoid dermatitis.

It is necessary to explain to a patient who attributes his disease to emotional strain that this is only a contributory factor and to offer him a thorough understanding of his problems whether they are occupational, financial or marital. In the case of the housewife afflicted with eczema of the hands, a careful discussion of her household chores, and ways and means of improving the efficiency in her work in order to reduce exposure to irritants, at the same time permitting some short rest periods, should be offered. This "office" psychiatry together with a prompt therapeutic result will be sufficient in most cases, but the use of ataractic medication will be necessary in some cases to restore sleep and emotional equilibrium.

SUMMARY AND CONCLUSIONS

The clinical features of nummular eczema justify its concept as a distinct entity. Its pathogenesis differs fundamentally from contact allergic type of eczematous dermatitis, atopic dermatitis and infectious eczematoid dermatitis. The dermatitis of the hands of housewives is a variant of nummular eczema. Both conditions have intrinsic and extrinsic causes,

which can be demonstrated by clinical study and the use of the alkali neutralization test of Burckhardt.

The physiology of alkali neutralization and the H ion concentration of the skin is discussed.

A rational therapy of nummular eczema and dermatitis of housewives is recommended.

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CALCIUM-POTASSIUM GLUTAMATE IN THE TREATMENT OF ASTHMA WITH COMPLICATIONS

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CALCIUM glutamate was found by Epstein and Sevag to improve the clinical condition of difficult asthmatic patients. This observation seemed particularly interesting because the basis for selection of the patients for their series was inability to respond adequately to specific anti-asthmatic therapy. When the glutamate was added to previous treatment there was a reduction of volume and viscidity of expectorate and a subsidence of chest rales. Subsequently, the patients were more resistant to the development of acute episodes and were better able to rid themselves of acute attacks when they did occur. A dose of 3.0 gm a day given over long periods of time was found to have persistent effects in patients followed for as long as three years. A small addition of potassium was found to enhance the clinical effect.

On examining the case records presented by Epstein and Sevag, it was discovered that all patients had considerable lung pathology and moderate to severe chronic asthma. Acute exacerbation occurred with exposure to an irritant or with upper respiratory infection, and the acute episodes did not respond well to specific therapy such as bronchodilators, antihistamines, iodides, et cetera, nor to the steroids. When glutamate was added to therapy, asthmatic rales were lessened or disappeared and vital capacities, where reported, increased in each case. When an episode was triggered by an upper respiratory infection, control of the asthma was not achieved until the infection had been brought under control. But in contrast to placebo treatment, the glutamate made it possible to regain the basal asthmatic status promptly when the temperature had been brought to normal. If old asthmatic patients such as these who are incapacitated for weeks at a time in their present environment and who are unable to change their environment, can be made to respond to asthmatic therapy, we would be able to facilitate their care and, in some cases, prevent loss of productive time.

A study was undertaken to see first if poorly controlled cases responded as well in our hands as those in the published report, and secondly, to determine the effect of the preparation on non-selected asthmatic patients. This paper presents our findings over a period of eighteen months with a combination tablet of potassium and calcium glutamates.

MATERIALS AND METHODS

Forty-four unselected asthmatic patients of all types were started on calcium potassium glutamate (Capomate) for periods of two to eight weeks.

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TABLE I.

Patient	Age	Sex	Duration of Asthma	Severity of Asthma		Sputum		Comments
				Before	After	Before	After	
1 (S.C.)	58	F	11 yrs.	Severe. Continuous every day, very bad with a cold	Severe 3 or 4 days at a time, every 8-12 weeks	Thick, white, tight, moderate	Thin, clear, tight, slight	The patient will not follow instructions and only takes ℞ during episodes. Response to ℞ is in 3 to 4 days. Dose 2 tablets Q.I.D. Duration of Capomate treatment 18 months. Has not required hospitalization since ℞.
2 (J.D.)	50	M	16 yrs.	Very severe. Continuous every day	Mild to moderate every day in the morning	Thick, white, copious, tight	Thin, clear, copious, loose	No severe or prolonged spells since taking 2 Q.I.D. for the past 8 months.
3 (C.V.)	58	F	? a few yrs.	Very severe. Almost constant	Mild. Almost cleared	Thick, white, slight	Watery, clear, slight	No emergency since on Capomate. Patient was hospitalized for 3 weeks prior to start 3 months ago.
4 (J.K.)	69	M	7 yrs.	Very severe. Continuous	Mild. Daily on exertion	Thick, clear, slight, tight	Thin, clear, copious, loose	Quite comfortable except on exertion. All medication except Capomate withdrawn. Dose 3 Q.I.D. for 7 months.
5 (R.M.)	58	F	4 yrs.	Daily with very severe weekly episodes lasting 2-3 days	Daily, moderate, continuous	Thick, clear, copious, tight	Thick, clear, copious, loose	Has had no severe attacks since one month after starting Capomate 9 months ago. Takes 2 Q.I.D. at sign of tightening or tension and less in between.
6 (E.B.)	65	F	18 yrs.	Moderately severe episodes several times daily	Slight improvement	Thick, moderate	Thinner, more volume	Patient started at 2 Q.I.D. and cut to 1 Q.I.D. Has been on Capomate 4 months.

TABLE I. (CONT'D)

Patient	Age	Sex	Duration of Asthma	Severity of Asthma		Sputum		Comments
				Before	After	Before	After	
7 (H.C.)	66	F	25 yrs.	Moderate, intermittent asthma	Slight improvement	Slight	No change	Patient reports feeling better on 1 Q.I.D. for the past 3 months.
8 (C.A.)	39	F	10 yrs.	Severe episodes every morning	Less severe episodes but still every morning	Thick, white, very voluminous	Watery-clear, slight	During the severe episodes there is a great deal of pain. She has taken the tablets for 6 months but does not adhere to the 2 Q.I.D. schedule. Starts taking tablets when painful cough starts again.
9 (S.B.)	50	M	Since childhood esp. with colds	Constant with continuous hard coughing	Improved	Thick, white, slight	Not much change	In 3 months at 2 Q.I.D. slow progressive improvement except periods of exacerbation during warm, humid weather. Has extensive lung damage and cannot be comfortable without Capomate. The hard cough has been moderated.
10 (J.K.)	67	M	Since infancy on exertion	Continual, with very severe episodes	Daily for 2-3 hours in the A.M. Severe	Thick, white, tight, slight	Thin, clear, loose, copious	Uses one tablet Q.I.D. for one week and 2 Q.I.D. the next. Feels this gives better relief than continuous dose. Says could not manage without ℞. Has been using 12 months. The continuous incapacitating cough is now occasional and of short duration.
11 (W.C.)	63	M	Since World War I (Service-connected)	Continuous, very severe every day	A few hours moderately severe every morning	Thick, white, slight, tight	Thin, clear, very voluminous. 1 hr. in A.M. loose	Has not obtained equivalent relief with any other drugs. Continues on Metacortin almost daily. Has trouble every morning but few prolonged sieges since starting Capomate 2 Q.I.D. 16 months ago.
12 (M.K.)	58	F	Many years	3 to 6 severe attacks a year lasting 7-10 days. Often hospitalized	No change	Clear, thin, moderate amount	No change	Says the medication helps but no evidence on examination. Stops taking ℞ as soon as emergency over. A strong psychic element? Has had tablets for 10 months. Takes 2 Q.I.D.

The patients were continued on previous treatment which included bronchodilators, iodides, theophylline drugs, antihistamines and corticosteroids. Eight tablets a day of Capomate were given, two before each meal and two at bedtime. Each tablet contained 350 mg of calcium glutamate and 150 mg of potassium glutamate.

Twelve of the patients were continued beyond the eight-week period and have now been followed for periods of three to eighteen months. In this group, the patients had definite lung pathology including moderate to marked emphysema, chronic bronchitis and bronchiectasis and history of repeated episodes of upper respiratory infection. There were seven women and five men; the ages ranged from thirty-nine to sixty-nine; and the duration of their asthma ranged from four to over fifty years. All have been receiving hyposensitization for offending allergens. During acute episodes, steroids have been given and some patients have had large doses given daily for long periods.

Patients were evaluated weekly for the first several weeks and then at longer intervals if their condition permitted less frequent office visits. They were instructed to vary their Capomate dosage according to effect. If there appeared to be no benefit, the dose was increased to three tablets Q.I.D., and if their condition improved, they were allowed to reduce the dose to one tablet Q.I.D., or less.

RESULTS

Twelve of the forty-four unselected asthmatics were improved subjectively or objectively within a period of two to four weeks. These patients were chronic asthmatics in poor condition at the start of the series.

The remaining thirty-two were unchanged when followed for the same period. Twenty-nine were patients with mild asthmatic involvement whose acute episodes could be controlled readily by accepted methods. The remaining three were patients who developed severe acute attacks on a psychogenic basis and had failed to respond well to any treatment. Trial periods of one to two months of glutamates failed to influence the course of their asthma.

The twelve patients who have been taking potassium and calcium glutamates for more than three months showed some improvement, usually in the modification of continuous severe asthma or prevention of frequent severe episodes superimposed on a mild continuous asthma. Rales lessened and the tenacity of the sputum was modified. Patients with severe and painful episodes of coughing showed marked improvement. The chronic asthmatic individuals who were not responding well to therapy at the start of the study are included in the table, with the exception of the three patients with strong psychic overlay who did not respond and were withdrawn after a one or two-month trial period.

Eight of the twelve patients have had excellent subjective and objective

improvement. Four patients, who could have been considered pulmonary cripples, have been rehabilitated to a point where they are comfortable and can return to some activity (Cases 4, 9, 10, 11). Two had frequent attacks of colds and bronchitis which precipitated very severe asthmatic attacks, often requiring hospitalization. Neither has been hospitalized since using the glutamates for periods of eighteen months (Case 1), and three months (Case 3). Cases 2 and 5, who had severe prolonged spells prior to starting the medication, have had no severe episodes since they have been on Capomate therapy (eight months and nine months). Case 5 points out the slow onset of effect because prevention of the patient's severe periods did not occur until he had been on treatment for a month.

Three patients (6, 7, 8) did not take an optimal dose, although each apparently was helped. Their response could be classified as fair to good. Case 7 is a "borderline" type of case with intermittent asthma. No striking benefit was seen in her or in others with the same degree of involvement. Finally, Case 12 was continued on the glutamates because she insisted she felt better; however, on examination, no improvement could be seen. She was typical of the patients with major psychic causation, none of whom have responded well.

In the entire group of forty-four, only one reported any side effects. This was a woman who was nauseated by the tablets which she said were too big.

DISCUSSION

The patients in this series who responded well were those who had either continuous or long-lasting episodes of severe asthma. In the latter, the removal of the precipitating factor had not resulted in relief by asthmatic therapy. The action of the glutamates in these patients was first to change the character of mucus from a thick, heavy, tenacious semi-fluid to a thinner free-flowing fluid, and second, perhaps as a result of this, to enable the patients to respond to accepted methods of control. When an acute attack was precipitated by an irritant or an infection, the asthma could be treated and controlled when the insulting factor was removed.

Several of the patients in the group who have stopped taking the glutamates have deteriorated and have then started taking the tablets again. In each case improvement was more rapid the second time, possibly because the patients had not deteriorated to their pretreatment levels. It has been necessary to stress to all patients that even though they feel better and are able to do more, they still have severe asthma and must continue their treatments.

The poor response of patients whose acute episodes were believed to be on a psychogenic basis may be because it was not possible to remove the precipitating factor. In Epstein and Sevag's Case 9, a similar patient is reported. A woman who had shown some improvement when on a first

course of glutamate, failed to respond when her asthma became aggravated by emotional agitation. Other cases from the previous report are paralleled in this series. For example, their Case 7 typifies the patient whose acute flareup responded to treatment when the irritant, in this case coal gas, was removed. Prior to glutamate treatment, an irritant-induced attack did not subside for weeks after the exposure.

An improvement in response to specific symptomatic treatment in poorly controlled patients was noted by Fenton[2] when he added glutamates to their treatment. He commented that his first reaction had been negative because there were no striking changes in any of ten patients who were given Capomate. On reviewing the records of these patients, however, seven had improved slowly and gradually while on the drug and had reverted to their former condition after the glutamates were withdrawn. Two did not improve, and the third did not relapse after withdrawal.

The mechanism by which the glutamates assist the chronic asthmatic patients was postulated by Epstein and Sevag to be a conditioning of the bronchial cells so they can act in a more normal manner. They reasoned that increased permeability of bronchial cell walls led to loss of potassium into the extracellular fluid, and that the depletion of the cell adversely affected the resistance of the patients. When they analyzed bronchial aspirates, those from asthmatic patients were found to contain twice as much potassium as aspirates taken from patients with carcinoma of the lung or with non-cancerous lung lesions. This confirmed the increase of cell permeability with subsequent loss of potassium and probably other intracellular elements in patients with chronic asthma. Calcium glutamate was given on the premise that the salt would deliver calcium to the bronchial region where it would substitute extracellularly for potassium and thus protect against dissipation of potassium through the cell wall. Serial analyses were done on the aspirates of four patients with long standing asthma. Over a period of one to six months, potassium in the aspirates fell and remained low during therapy with calcium glutamate but rose promptly when a placebo was substituted. The placebo was calcium gluconate, in a tablet containing the same amount of calcium as in the glutamate tablets; hence, the effect was not that of the calcium ion alone.

The mechanism propounded by Epstein and Sevag is interesting. There may be a predilection of calcium glutamate for bronchial tissue; or the effect may be a general glutamate action, inasmuch as no control work has been done to rule out the eventuality. The potassium content of bronchial secretions did decrease when calcium glutamate was given, so that there is objective laboratory evidence of a change in the non-responsive patient. The added effect of a moderate amount of potassium was a clinical impression, but it stands to reason that there would be an excessive loss of potassium in a patient who has excessive levels in the bronchial fluids.

CONCLUSION

Patients with a history of chronic bronchial asthma, lung pathology, and poor response to usual forms of treatment can be helped in most cases by adding calcium-potassium glutamate to their therapy. Patients who respond well to treatment do not show any enhanced response when the glutamates are given. The glutamate, therefore, must be considered an aid in the treatment of asthma rather than a specific therapy, but a very valuable aid in complicated patients. On the basis of this study and of the previous paper by Epstein and Sevag, it is not possible to conclude definitely that the patients who responded well to standard asthmatic therapy cannot be helped by Capomate. With the criteria used, they were not, but a study designed to test the resistance to acute episodes should be undertaken before it can be stated flatly that it is of no value. However, it did not by itself prevent or influence an acute episode in the patients who responded to standard remedies.

SUMMARY

Chronic asthmatic patients, whose acute episodes did not respond well to treatment, were given calcium and potassium glutamates in addition.

Thick mucus was loosened, rales decreased, and hard painful cough was eased. Response to the usual anti-asthmatic measures was improved, and the patient's condition and activity was bettered. The frequency and severity of acute episodes was lessened.

Patients whose asthmatic attacks responded adequately to the therapy they were receiving did not respond better when the glutamates were added.

The glutamates (Capomate) are helpful in the management of difficult patients. These findings are in accordance with those of two other investigators.

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THE MASTER-WORD

Although a little one, the master-word looms large in meaning. It is the "Open Sesame" to every portal, the great equalizer in the world, the true philosopher's stone which transmutes all the base metal of humanity into gold. The stupid man among you it will make bright, the bright man brilliant, the brilliant student steady. With the magic word in your heart, all things are possible, and without it all study is vanity and vexation. The miracles of life are with it; the blind see by touch, the deaf hear with eyes, the dumb speak with fingers. To the youth it brings hope, to the middle-aged confidence, to the aged repose. True balm of hurt minds, in its presence the heart of the sorrowful is lightened and consoled. . . Not only has it been the touchstone of progress, but it is the measure of success in everyday life. . . . The master-word is *work*.—SIR WILLIAM OSLER.

FURTHER OBSERVATIONS WITH ANTIHISTAMINES IN REDUCING REACTIONS IN INTRAVENOUS PYELOGRAPHY

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THIS continuing study, started in 1952, covers more than 2,000 cases of intravenous urography. An attempt was made to minimize reactions to the contrast media by the addition of injectable antihistamines. A previous report of 1,000 cases is noted,[16] and an additional 1,200 cases were added to the series. More than 600 patients were studied with the double blind technique using injectable Chlorprophenpyridamine Maleate (Chlortrimeton Maleate, Schering) 20 mg, or injectable Parabromdylamine Maleate (Dimetane Maleate, Robins), 20 mg. An additional 500 cases received either 20 mg of Chlor-trimeton or 10 mg of Dimetane.

Reaction to any injectable drug is a constant hazard which is encountered in therapeutic and diagnostic procedures.[3,6,8,14,17]

The ever-present danger of severe or fatal reaction to intravenous pyelography has been a constant spur to investigation. Pendergrass and his co-workers, Perillie & Conn, and Killman and his co-workers recently reported deaths from intravenous pyelographies.[10,13,14] Many investigators have reported on new urographic media with somewhat reduced reactions to the dye.[5,12,18,24] However, no drug in use at present is without potential danger.[9,11,22] Simon, Winter and Wechsler[19,21,23] and others have attempted to reduce reactions with the use of oral and injectable antihistamines. Some investigators were of the opinion that allergy is a contradiction to pyelography.[4] Others differed on the value of preliminary skin and ocular tests.[1,2,15,18] Zeitel and his co-workers[24] stated:

"Preliminary skin and ocular tests are of no value in screening for allergic reactors. Intravenous tests were done in 1,000 patients with only one positive result. In this patient (asthmatic), a severe systematic reaction followed intravenous injection of 1 cc of Renografin. The examination was discontinued. As a screen procedure, intravenous testing is of limited worth, since only 1 in 1,000 may be expected to react."

He concluded by saying:

"Perhaps in persons with a history of allergy, use of a preliminary intravenous test dose may decrease the possibility of flooding the blood stream with a large amount of noxious allergens."

Mullen and Hughes[12] stated:

"Intravenous testing was of no value in detecting reactions. It is doubtful if any of the present day methods of testing can predict serious or fatal reactions."

Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, on March 18, 1959.

Pendergrass stated in his comprehensive review of 106 urographic fatalities which occurred in the United States and Canada from 1942-1957:

"Pretesting for hypersensitivity has been of no practical value in our hands. A negative sensitivity test should not be permitted to give the attending physician a false sense of security. Negative sensitivity tests were recorded in most of the 'immediate' fatalities reported by us. As has been noted by Trottnen and his associates severe reactions may be precipitated by the intravenous injection of only a small amount of 10 per cent solution of contrast medium. We know of instances where a severe reaction in the eye followed a conjunctival sensitivity test.

"One physician reported that he had recently encountered a profound 'Anaphylactoid' reaction to only 0.1 cc of intracutaneous Hypaque; the patient went into severe shock and recovered only after being maintained for some time on Levophed. Failure to do pretesting is not to be regarded as neglecting the welfare of the patient. It should be emphasized again that 'A careful clinical history, with particular emphasis upon allergy, and studied clinical judgment still remain the sine qua non in the field of medical practice.'"

The addition of antihistaminic agents to injectable mixtures has met with resistance from many sources. Some investigators feel that anaphylactic or fatal reactions may be delayed by the antihistamines and occur at a time when the patient is away from the physician's office. Others feel that no benefits are derived from such mixtures, and that toxic phenomena induced by the antihistamine itself may occur. These sober comments cannot be lightly dismissed. Nevertheless, in over seven years of observation, and more than one thousand cases of antihistamine-drug injections, this investigator has yet to see a delayed anaphylactic or toxic reaction in any patient, except for an occasional transient dizziness or sleepiness. We therefore concluded that the use of antihistaminic agents had a place in the prevention of drug reactions.

A number of investigators found that injection of an antihistaminic agent preceding or in conjunction with the contrast dye reduced reactions. In most cases the reports covered a limited number of reactions, such as urticaria, nausea, vomiting, heat and shock, and the studies were often uncontrolled. To overcome these valid objections, a double blind study was instituted. Shortly thereafter, a new antihistamine suitable for intravenous injection, Dimetane Maleate, became available for inclusion in our study.[7,20] We were able therefore to compare its effectiveness with that of Chlortrimeton. As in our previous report, asthmatic and allergic individuals were not excluded. Patients with mild, moderate or severe reactions during previous pyelography were noted and specifically included in this study. Five patients had a history of severe reactions, and eighty patients had mild or moderate reactions. One patient, who had had a coronary two months previously, was also included.

PROCEDURE

The contrast medium used throughout was Urokon, with 20 to 25 cc being drawn into a 30 cc syringe, and 1 cc of a specially prepared solution of Chlortrimeton maleate 20 mg, or a specially prepared solution of 10 mg of Dimetane maleate, added. In the double blind study, only 20 mg solutions of each antihistamine was used. The solution was then rapidly injected into the basilic or median vein, and the reactions of the patient were recorded. In the double blind study, solutions had special code numbers unknown to the operators. Only after all the results were tabulated, were the code numbers revealed.

TABLE I. DISTRIBUTION OF ALLERGIC INDIVIDUALS IN THE SERIES
(1202 Patients)

Type of Allergy			Double Blind			Total
	Chlor-trimeton (20 mg)	Dimetane (10 mg)	Chlor-trimeton (20 mg)	Control	Dimetane (20 mg)	
Number of patients	326	196	331	234	115	1202
Asthma	3	3	6	3	2	17(1.4%)
Hay fever	10	12	15	13	4	54(4.5%)
Food allergy	6	3	2	2	2	15(13%)
Eczema and mixed allergy	8	17	10	8	3	46(4%)
Penicillin allergy	7	8	8	4	4	31(2.6%)

DISCUSSION

Table I gives the distribution of allergic individuals in our series.

No selection of patients was made. There were approximately the same percentage of allergic individuals in the group receiving injectable Chlortrimeton as in the group receiving injectable Dimetane. There were 158 known allergic individuals in the series, which included seventeen asthmatics, fifty-four patients with hay fever, fifteen patients with food allergies, forty-six with eczema, urticaria and mixed allergies, and thirty-one known to be allergic to penicillin. It is interesting to note that none of the protected patients had any severe or even moderately severe reactions. One patient, who had experienced an asthmatic attack following a previous IVP, was free of symptoms when given the dye-antihistamine mixture. Another patient had a severe angioedema of the face during a previous IVP. When given the mixture described, he had a few urticarial wheals on his face that cleared spontaneously in about ten minutes. However, in the control group, three patients had severe (anaphylactic) reactions and five patients had moderately severe reactions.

Table II compares the results in the present series with those previously recorded in a table compiled by Dotter, Wetschler and Steinberg, who recorded reactions to contrast media in angiocardiography. It is interesting to note that the reactions were reduced in both Urokon-antihistamine mixtures, although in the latter instance only 10 mg of Dimetane was used. In fact, it appeared that when the smaller amount of Dimetane was

TABLE II. DISTRIBUTION OF ALLERGIC INDIVIDUALS†

Symptom						Double Blind		
	Dotter et al	Control	*Chlor-trimeton (20 mg)	Chlor-trimeton (20 mg)	Dimetane (10 mg)	Chlor-trimeton (20 mg)	Control	Dimetane (20 mg)
Heat	100%	57%	30%	35%	34%	39%	61%	21%
Weakness	80	16	12	11.5	10	10.5	11	10
Headache	32	3	5	3	3.5	6	9	6
Nausea	40	33	16	11	11	20	26	11
Vomiting	12	10	2	4	1.5	7	11	4
Coughing	44	13	5	2	1	7.5	14	8
Thirst	72	16	11	8	6.5	8.5	14	3
Urticaria	20	3	1	1.5	0	5	6	4
Arm pain	20	10	5	7.5	8.5	10	15	8
Flush	68	12	9	19	16.5	29	38	12
Pallor	28	1.5	3	7.5	2.5	2.5	5.5	1
Wheezing	4	1	0.2	1	1	6.5	7	0
Sneezing	4	1	0.2	0	0.5	1.8	5.5	3
Itching	24	3.5	3	2	2	4	3	0
Palpitations	24	4	11	2.5	6	3	4	2

†This table compares the results in our series with a similar table compiled by Dotter, Wetchler, and Steinberg, who recorded reactions in contrast media used in angiocardiography.
*As previously reported.

used, many of the irritating symptoms were observed less frequently. An occasional complaint of dizziness or sleepiness was reported by a few patients who received the antihistamine mixtures in the 10 mg strength. These symptoms usually were of brief duration. In only one case was it necessary for the patient to take a nap before he could drive home.

The most important feature of our study was the elimination of severe shock reactions and the reduction of moderately severe reactions. The overall reduction in reactions was fourfold or more. In addition, there was a reduction in the incidence and severity of toxic and irritation phenomena.

Psychogenic reactions are always difficult to evaluate in the patient. The level of anxiety in the technician or physician who is performing the IVP is even more difficult to determine. It is my opinion that the physician or x-ray technician often transmits his anxiety to the patient and thereby increases the untoward symptoms in the patient, quantitatively as well as qualitatively. It was therefore interesting to observe the reduction of anxiety in both the x-ray technicians and physicians when the antihistamine mixtures were used. The net result was a reduction of anxiety and symptoms produced by anxiety, such as they may be, in the patients of this series. During the double blind studies, however, there were two instances when patients presented histories of severe anaphylactic reactions to previous IVP's, and a new technician insisted that these patients be eliminated from the study and be given the Dimetane mixture. This was done and no reactions occurred.

CONCLUSIONS

1. Mixtures of Urokon with Dimetane or Chlor-trimeton resulted in a significant reduction of reactions in intravenous urography.

2. Parabromdylamine Maleate (Dimetane Maleate) in 10 mg dosage was at least as effective as Chlorprophenpyridamine Maleate (Chlortrimeton Maleate) in 20 mg dosage for intravenous use. In fact, a greater reduction of side effects was noted even though a smaller quantity of drug was used.

3. A history of allergy was not found to be a contra-indication to urography when this procedure was used.

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HOW PERCENTAGES MAY BE MISLEADING

Expressing changes in percentages often leads to completely erroneous conceptions of the actual magnitude of the changes involved. For example, if the population of a certain region has increased 600 per cent, the change involved appears to be of considerable magnitude; actually it may be quite insignificant, for if the original population of that region consists of only three inhabitants, an increase to 21 inhabitants would be a 600 per cent increase. If, instead of expressing the change in percentage, we had simply stated that 18 more people have moved into the locality, the impression of a change of great magnitude would have been avoided and a much truer picture of the actual situation would have been obtained.

How misleading a statement of changes in terms of percentages can be may be seen also from the following facts disclosed by a congressional investigating committee in 1933. In 1931, Great Britain devalued the pound sterling. Certain American producers feared that this might give their British competitors an undue advantage in the American market; they therefore asked for tariff protection for their own American-made goods. In support of their argument they showed that within a very few months after the devaluation of the pound sterling imports from the United Kingdom into the United States had "surged upwards." Imports of canned salmon were up 2500 per cent; imports of pig iron had risen 611 per cent; and long-staple cotton imports had increased 1238 per cent. These figures were impressive indeed and seemed to prove the point which the American producers hoped to establish. The actual situation, however, was far from alarming. Imports of canned salmon had increased only 44,000 pounds—a mere trifle compared with the 300,000,000 pounds produced in American canneries. The 611 per cent increase in the imports of pig iron represented a total of 460 tons—hardly a threat to American pig iron production; and the 1238 per cent increase in the imports of cotton represented goods valued at no more than $982.00.—W. H. WERKMEISTER, "An Introduction to Critical Thinking," Johnsen Publishing Company, Lincoln, Nebraska, 1948, pp. 554-555.

ALLERGIC RHINITIS DUE TO PLASTICS

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PLASTICS or resins have invaded everyday life. It is impossible to look around you without encountering plastic articles. Everything from dentures to pessaries, furniture and fabrics to food wrappings, is made of plastic. Phenol-formaldehyde and urea-formaldehyde resins or plastics are made, in general, from cellulose (wood flour) and volatile compounds such as formaldehyde, phenol, and vinyl ethers. They are manufactured or molded with or without heat or pressure. Some are completely cured or polymerized and rarely give off any odor or vapors, but some (perhaps incompletely cured) do give off a formalin-like odor. Frequently this odor may be noticed when unwrapping new plastic articles, such as fabrics, furniture, playing cards, or new eyeglass frames. The following is a report of a patient who developed an allergic rhinitis due to plastics.

CASE REPORT

J. B., a woman bank teller, aged thirty-seven, was referred by an otolaryngologist because of allergic rhinitis. The patient had been having trouble for approximately five to six weeks, consisting of stuffiness of the nose, sneezing, and running eyes, which was associated with eating.

Family history was entirely negative for allergy. The patient had never had any allergic symptoms previously.

Physical examination gave negative findings except the mucous membrane of the nose which looked typically swollen, pale, and moist. The patient's eyes were red and she had some postnasal drip.

A nasal smear showed 24 per cent eosinophilia. The blood count was essentially normal with a 13.9 gm hemoglobin and an 8,000 white cell count. A differential count showed one basophile, seven eosinophiles, fifty-five segmented forms, thirty-two lymphocytes and five monocytes. The red cells were within normal limits. Urinalysis was negative.

The patient had fairly complete intradermal skin tests including inhalants, common foods, grasses, fruits, vegetables, and nuts. She showed a few plus-2 tests to such things as cat, dust, oats, tea, some fruits and a few vegetables in 1:1,000 dilutions, but on the whole her skin tests were not significant although the foods had to be considered. She took no drugs except an occasional Ex-Lax.

She was seen two weeks later, having been given 50 mg of Perazil in the morning and at night, and Vasocort nasal spray. One week later she was still having trouble but not quite so much. She did not smoke. There was no connection with paint or fumes, cosmetics, soap or shampoo, but it was discovered that she was always better outdoors. She seemed to have symptoms while eating at home. She was told to eat out, which she did, and the symptoms disappeared. She returned home for meals and the difficulty began again. She was then told to eat in a different room, and had no trouble. By this time she discovered that a new plastic tablecloth on the kitchen table, which gave off a formalin-like odor, was the cause of her allergic rhinitis. The cloth was removed and the patient was cured. Nasal smear on May 7, 1957 showed no eosinophiles. The patient has had no recurrence.

Keene Clinic, 331 Main Street
Submitted January 9, 1959

SHALL WE CHANGE OUR NOMINATING PROCEDURES?

ELOI BAUERS, LL.B.
Minneapolis, Minnesota

THERE are two fundamental principles underlying American parliamentary law and upon which it is built. The first of these is that the rights of all members in every group must be respected. This means not alone the rights of the majority, but also those of the minority, the individual, and even an absentee member. Second, the rights in common of all the members in any group must be protected against hurried or ill-advised changes in its constitution and by-laws, which are the fundamental rules it has adopted to define the duties and privileges and regulate the conduct of its membership. Because we are herein concerned with a situation that is quasi-legal in character, as Counsel for the College, I have been asked by its Board of Regents to prepare this article for publication in the ANNALS.

Yours is a national society composed of qualified physicians and scientists interested primarily in promoting and advancing the study and clinical knowledge of allergy. You are not a group of persons essentially politically-minded, nor are your members, in the main, skilled parliamentarians. All of you do recognize and observe the duty you have in common to support the principle of equality of rights and privileges for all, and its corollary, equality of duties and obligations, in your group relations with one another.

The College is a non-profit organization established and existing under and by virtue of the laws of the State of Minnesota. It convenes annually for such social, intellectual and scientific purposes as are authorized by its corporate charter; it transacts most of its corporate business during these conventions, and it elects the officers and boards which will control and manage its business affairs until its next annual meeting.

Under its by-laws, these annual elections are required to be by ballot, with a majority of the votes cast necessary to elect. Pursuant to the rules of procedure uniformly adopted by most of the larger national medical societies, nominees for the elective offices and boards in the College are selected by a Nominating Committee which, under the regulations creating it, meets during a prescribed period of time preceding each annual meeting within which it must select and report a single election slate, one nominee for each office and board position to be filled. This slate, or ticket, when its selection is completed and reported within the time prescribed, becomes the official ballot. It has (and this is important) the same effect as though the nominees listed thereon were actually nominated from the floor. Further nominations, both by petition and from the floor, are also permitted under our by-laws. Whenever any additional

nominations are made, the names of such nominees must be added to the list of names reported by the Nominating Committee, and submitted to the voting members before the voting gets under way and balloting begins.

Most national societies similarly made up of members residing in widely separated geographic areas, where the qualifications and talents of one group are not too well known to many of the others, have found after long experience that the selection of a slate by a nominating committee and election by ballot are the most successful election procedures. It is the method with which we are all quite familiar, because it is the one always followed in conventions we customarily view on our television screens or read about in the public press. Briefly, it presents these advantages:

1. A nominating committee possesses greater opportunity for more thorough investigation of prospective nominees and can better determine their qualifications, fitness and capacity for performing the duties and responsibilites of the offices or board positions to be filled.

2. It has ample time and opportunity to interview the nominees under consideration, not only to learn if they will accept, but to ascertain in advance their willingness to give whatever time may be required to attend meetings and to undertake all of the responsibilities which conscientious service will require of them, if elected.

3. It can apportion representation more equitably among groups having divergent viewpoints resulting from diverse geographic, philosophic, scientific and economic backgrounds.

Article V, Section 7(j) of our By-Laws, revised and published in January, 1959, prescribes the nominating and voting procedures now in effect. It deals with the selection, functions and duties of the Nominating Committee; its duty is to report the official slate when it has completed the selection thereof; it defines the manner and method of giving notice thereof to all voting Fellows; it provides for additional nominations by petition, and also from the floor; and finally, it directs how voting is to be conducted and dictates the vote required for election.

In its present form, this section of the By-Laws is the result of an extended process of development during which it has been rewritten, altered and amended many times and in many ways by successive By-Law Committees during the sixteen years since I prepared the original Charter and By-Laws. From its beginning, the College has adhered to the basic democratic principle that all of its voting members are to be eligible for election to any of its offices and boards without any other distinction than that created by their respective talents and qualifications, in the expectation that only those best qualified by training and experience will usually be elected. Down through the years, it has been the consistent practice

of the Board of Regents to assure all voting members an equal voice in the selection of its elective officers; and whenever any changes have been proposed in our election processes, great caution has always been exercised to make certain that the By-Law amendments required to effectuate the same did not conflict with this basic concept.

During our annual business meeting in 1958, the fairness and equity of these procedures were openly challenged, and the complaint made that some members now feel they are denied the equal representation and voice in College affairs to which they are entitled.

On the following day, April 22, 1958, at its annual meeting, the Board of Regents appointed a special committee of five of its number to consider the changes proposed in our nominating procedures and to report back to the Board such suggestions for improvement in our elective processes which the committee might consider to be desirable and in the best interests of the College. This special committee of five found the methods and procedures now in use to be fundamentally sound and recommended they be retained in force and effect without any change or amendment therein or thereto. The committee also reported that if the selection of the official slate is actually made in strict conformity with the terms of Article V, Section 7(j) of the By-Laws, its provisions for additional nominations, both by petition and from the floor, afford an adequate and effective remedy to any and all members who may object to the nominees listed in the official slate, and full and complete opportunity for the unrestricted exercise of recognized democratic processes in the election to follow.

That the findings of this committee, and the conclusions reached in its report, were fundamentally sound was clearly revealed to all members at the annual election of officers and Regents held during the business meeting of the membership in San Francisco in March of this year. The presiding officer, President Merle W. Moore, read the report of the Nominating Committee, saying as he did so that the nominees for each office listed on the official ballot were now placed in nomination. He followed this with a separate announcement as to each office, beginning with the highest, that nominations from the floor were in order and would be received by the chair.

Although full opportunity was given for further nominations as to each elective office in succession, it was only for the office of Second Vice President that such a nomination was, in fact, made. Following this additional nomination from the floor, President Moore promptly and correctly announced that the election to fill the office of Second Vice President would be by ballot. He thereupon appointed two tellers of election to pass out, collect, and count the ballots, and to determine the vote. After the tellers reported the results of the vote to the presiding officer, he announced that the member nominated from the floor, Dr.

Grace M. Talbott, had received the majority of the legal votes cast and promptly declared her duly elected to the office of Second Vice President.

It was a timely and obvious demonstration and, in my opinion, one so positive as to dispel forever any uncertainty or doubt that our current election procedures are both fair and equitable and furnish a real and effective remedy to any voting members who may be dissatisfied with, or for any reason object to, the nominees annually selected by our nominating committees. If, therefore, the charge were to be repeated today that "some members are denied the equal representation and voice in College affairs to which they feel they are entitled," it would now so obviously appear to be fanciful and frivolous that I am positive the membership generally would disregard it.

The election results in San Francisco must have made it apparent to all that the present Constitution and By-Laws of The American College of Allergists afford its membership ample scope for the unrestricted exercise of every right or privilege commonly recognized as essential to completely democratic elections.

2160 Rand Tower
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INDEPENDENCE, DIGNITY, AND ORIGINALITY

"And if in order to preserve your independence, your human dignity, you experience sometimes troubles, difficulties and all that follow, preserve your independence in spite of all and preserve it fiercely. The day will come when you will congratulate yourself for having done so. Of course, you will not be granted official honors, social prestige and all the vanities which you would have bought at the price of freedom of thought. Be not affected nor depressed by it. The day will come when you will be infinitely happy about it.

Preserve your originality. It is the result of the gracious and beneficial influence that your parents, your friends, the people of your home town have exerted on you. In respect and gratitude to them, preserve your originality; you owe it to them.

Preserve your originality. It is this that will give your scientific work its frankness, its grace, its elegance, its warmth and life among so many artificial, banal, commonplace, cold, and corpse-like works, for originality—is the colorful bonnet of the girls of Anjou among the banal Parisian hats."—Maurice Arthus, Philosophy of Scientific Investigation, Baltimore, The Johns Hopkins Press, 1943.

PRINCIPLES OF THERAPY IN HUMAN HYPERSENSITIVENESS

Historical Document

ROBERT A. COOKE, M.D.

. . . Under the general title of hypersensitiveness we group those reactions occurring in man and in the lower animals that are characterized by specific symptoms to specific substances which are of themselves devoid of reaction in the normal of the species.

Included in this group we recognize at once the phenomenon of anaphylaxis as seen in the experimental animal, because here we have specific symptoms to specific substances called antigens to which the animal has been sensitized. The important phenomena of anaphylaxis I shall list briefly in order to contrast them with another form of hypersensitiveness which we see in man and to which we now apply the term *allergy*.

I. Anaphylaxis is always artificially induced by the preliminary injection of a minute sensitizing dose of a substance which, when reinjected after a lapse of from five to ten days, produces anaphylactic shock with death in the experimental animal. The important point to bear in mind here is that the phenomenon is always artificially produced by an immunological process.

II. The antigenic substance known in anaphylaxis as anaphylactogen must be protein in nature.

III. The reaction in the experimental animal to the anaphylactogen depends upon the formation of antibodies that are specific to this antigen. These antibodies can be demonstrated as attached to certain cells, for example the smooth muscle fiber of bronchi and uterus. They also exist in a free form circulating in the blood and can be demonstrated by means of precipitin reactions, by complement fixation and agglutination, and most important still, by passive transfer.

IV. Anaphylactic hypersensitiveness is never inherited. By this I mean that the hypersensitive male guinea pig can never transmit to his offspring a direct hypersensitive state or a tendency to such a state.

V. Desensitization of the hypersensitive or anaphylactic animal can be accomplished by the sublethal injection of the specific antigen, after which time the specific antigen can be given in large quantities without the manifestation of any anaphylactic symptoms.

VI. Anaphylaxis in the animal is not permanent. The hypersensitive

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From the Department of Bacteriology and Immunology of Cornell University and the New York Hospital, First Medical Division.

rabbit loses its reaction in three weeks. The exception to this rule is the guinea-pig, in which the reaction is permanent for three years, which is the natural span of life for the animal.

VII. With regard to the degree of hypersensitiveness that is created artificially, it can be stated that a 250-gram guinea pig has been rendered anaphylactic with as small a quantity as 0.000001 cubic centimeter of serum or 0.000005 gram of crystalline egg albumin. The intoxicating dose of antigen varies from 0.1 to 0.01 cubic centimeter of serum when administered intravenously.

As opposed to this picture of the phenomena of anaphylaxis, I shall present that of hypersensitiveness as seen clinically in the human.

I. It is never and can never be artificially induced at will. By this I do not mean to infer that anaphylaxis as such cannot be induced in the human for the phenomena of this condition bear no relation to the clinical reactions that we see. Many instances are on record today of the fact that an individual reacts to certain substances the first time they are administered. This is best observed in the history of children or infants in which the first administration of egg or cows' milk induced violent manifestations of acute gastro-enteritis, asthma, or urticaria. On the other hand, we find that those individuals who have been given foreign proteins in the form of therapeutic sera do not react with characteristic symptoms in any such way as those who are *naturally* hypersensitive.

II. Hypersensitiveness in the human is in no sense restricted to protein, for, as you will see later, we have reactions occurring in the human to such non-protein substances as glue, iodoform, arsenic, aspirin, to mention a few of the many non-protein substances that have been met with.

III. Antibodies are not a demonstrable phenomenon. To be sure, antibodies can be demonstrated for a short time in the blood stream of humans who have received enormous doses of foreign serum; but they are not demonstrable in the blood stream of those cases of clinical hypersensitiveness even though this hypersensitiveness exists to true protein substances such as ovomucoid and casein and in spite of the fact that these individuals were receiving subcutaneous injections of these substances at the same time. To those substances that are non-protein in nature, antibodies, as we know them today, cannot be formed either in man or in the experimental animal.

IV. A very important phase of natural human hypersensitiveness is its dependence upon certain inherited traits or capacities. In a former paper with Dr. Vander Veer, the writer demonstrated, among others, the following facts with regard to inheritance:

(a) Of 504 cases of hypersensitiveness there was a positive antecedent history of hypersensitiveness in 48 per cent. Whereas, in another group

of apparently normal individuals the antecedent history showed hypersensitiveness in only 14 per cent.

(b) In those cases in which there was an inheritance of allergy on both sides the age of onset curve reached its maximum before the fifth year. Whereas in those cases in which the inheritance was unilateral the age of onset curve reached its maximum between the tenth and fifteenth years. In those cases in which no family history could be elicited and in which therefore, presumably, it was more distant, the maximum of onset did not reach its height until the twentieth to the twenty-fifth year.

(c) As to the nature of the inheritance it has been shown that the individual does not inherit a specific sensitization, since the offspring are not born sensitive, twins do not show the same clinical form of hypersensitiveness and the reaction in the descendant is more frequently different from than identical with that of the antecedent. The individual inherits a tendency or capacity for peculiar cellular activities and the factor that determines what form these activities shall take is not even surmised.

V. Desensitization in anything like the complete form that has been attained in anaphylaxis is utterly impossible in cases of clinical human hypersensitiveness. To be sure there is in a sense in the human a partial desensitization, better expressed as "clinical insensitiveness," as the result of subcutaneous injections of a specific reacting substance. But even in those cases in which, as the result of an overdose, constitutional reactions with asthma, urticaria or coryza have been induced, a similar injection on the same or the following day will produce similar phenomena of the same or even a greater degree of severity.

VI. In general the natural clinical human hypersensitiveness is a permanent condition. While a few instances of spontaneous cures have been recorded in hay fever and horse asthma, it is safe to assert that these are the extreme exception and that a person once hypersensitive to animal emanations is always hypersensitive. The exception to this is the reaction to foods occurring in infants. The majority of these cases lose their reaction before they reach adult life.

VII. While we can marvel at the delicacy of the reaction artificially induced in animals, it is nothing in comparison with the exquisite degree of hypersensitiveness frequently met with in man. One milligram of nitrogen in the form of serum is required to kill a guinea-pig weighing one-fourth of a kilo when administered intravenously, whereas 0.0025 milligram has produced violent constitutional reaction when administered subcutaneously in a hypersensitive man weighing 70 kilos or two hundred and eighty times the weight of the guinea pig. If this injection in the man had been given intravenously it would, without question, have produced death. In other words, the degree of hypersensitiveness in this case was nearly six hundred thousand times as great as any that has ever been artificially produced in an animal.

. . . We have under the general classification of hypersensitiveness two distinct groups which have been differentiated. First, an anaphylaxis artificially induced in animals to protein substances only, and secondly, allergy or human hypersensitiveness, a natural or spontaneous phenomenon occurring with protein or non-protein substances. There are only two points of similarity. (1) In man as well as in the animal the reaction is undoubtedly cellular and (2) there is a clinical similarity between the anaphylactic reaction in the guinea pig, shown by manifestations that can be called asthma, and bronchial asthma in man, which is merely one of the clinical manifestations of human allergy. I do not believe we can overestimate the importance of this distinction of the two conditions so generally confused. We see so constantly in medical literature, attempts to explain all phenomena of human allergy on the basis of the preconceived ideas of what might be expected from studies in anaphylaxis, whereas it must be evident to anyone who has worked thoughtfully in this field that the phenomena accompanying the two conditions are fundamentally distinct.

SYMPTOMS OF ALLERGY . . . The tissues that are involved in the reaction are those of epiblastic origin, particularly the skin and the mucous membranes of the respiratory and gastro-intestinal tracts. The symptoms that are produced are the result of congestion, edema, and secretory activity in the tissues affected. The hypersensitive area may be restricted to a small circumscribed space, such as the mucous membrane of the nose or of the stomach or of the bronchi, or even of the small portion of the skin. Or it may be widespread and include all of these tissues at one and the same time. To be more specific, the clinical complexes known to be allergic are allergic coryza (hay fever), bronchial asthma, acute gastro-enteritis, functional hyperacidity, intestinal angioneurotic edema, and certain forms of dermatitis. The reaction may be immediate, that is, it may occur from one minute to one hour after the introduction of the allergen or it may be delayed for twenty-four hours. For example, an individual who gives a perfectly typical clinical history of hay fever occurring in August and September and perfectly free at all other times of the year, immediately upon contact with the pollen of ragweed develops a most acute form of coryza. These immediate reactions are more readily diagnosed than the delayed reactions. As an instance of a delayed reaction there is the history of a woman who had suffered with urticaria and angioneurotic edema for six months. It developed in her history that during this time she had made a habit of eating a rather unusual amount of chocolate at luncheon each day in order to put on weight. It was discovered by skin test . . . and clinical experiment as well that chocolate was the only etiological factor in the production of her symptoms. After abstaining from this article for a week, during which time no manifestations developed, she was allowed to eat the usual amount

of chocolate at a certain time. Urticaria and angioneurotic edema developed, not immediately, but at the end of twenty-six hours, and this reaction time was identical in three separate tests.

Another manifestation of this delayed reaction is seen in what we call serum sickness, where urticaria develops from five to seven days after the introduction of such a foreign substance as horse serum, given for therapeutic measures. The discovery of the cause and its relation to the effect in these cases of delayed reaction is one of the most difficult problems with which we have to deal today in human allergy.

I have stated that the pathological conditions are congestion, edema and secretory activity. In addition there is an irritation of the sensory nerve ends, giving rise to the symptom, pruritus. . . . When the hypersensitive area is limited to the mucous membrane of the nose, the reaction that ensues in the presence of the specific allergen gives rise to those manifestations which we call hay fever. Where the hypersensitive area is limited to the bronchial mucous membrane the congestion and edema of this membrane create an interference with the free entrance and exit of air and we have the clinical picture of bronchial asthma. Where the hypersensitive area is limited to the skin, the reaction that occurs when the hypersensitive tissues are brought in contact with the specific allergen manifests itself in several forms, the reason for which we do not yet know, but it produces the clinical condition of either urticaria, erythema, or angioneurotic edema. When the cells that are hypersensitive to a specific allergen are diffuse and include the nasal mucous membrane, bronchial mucous membrane, intestinal mucous membrane, and skin, we have the clinical picture of disturbance in all of these areas.

. . . . We must discard the term *protein reaction* as entirely too restricted, and we must recognize the fact that any chemical element or compound in soluble form is a possible cause for an allergic reaction in some individual. To be sure, there are substances that are much more commonly met with than others and it has been possible in a general way and for purely clinical reasons to group these according to the usual channels of observation.

I. BY INHALATION. (*a*) *Animal Substances.* So far as we can see this is essentially limited to the dander, that is the epithelial cells that are desquamated from any animal. Those most commonly met with are the domestic animals, such as the dog, cat, horse, bird, rabbit, guinea pig, and they are very commonly met with as reactions to the goose, duck and chicken where the feathers of these animals are used in pillows.

(*b*) *Vegetable Substances.* These include the pollens particularly and portions of the leaves, stem, roots and seeds of various plants. The most important member of this group is the powdered root of orris, because it is used so extensively commercially in tooth powder and sachet.

This group of substances absorbed by inhalation is by far the most im-

portant in the causation of those forms of human allergy diagnosed as hay fever, vasomotor rhinitis and bronchial asthma. As a matter of fact they are the demonstrable cause in 62 per cent of all cases of asthma and in 80 per cent of all cases of allergic coryza, both hay fever and vasomotor rhinitis. . . . Our present concept of vasomotor rhinitis is that it is an allergic reaction, identical with hay fever but not seasonal in character on account of the fact that there is a more or less continuous exposure to the exciting cause and that therefore the symptoms are practically continuous.

II. BY INGESTION. Here we have a group of reactions occurring from substances artificially taken as (1) foods or condiments and (2) drugs. This group accounts for about 10 per cent of the cases of asthma and about 80 per cent of the cases of urticaria, angioneurotic edema and intestinal manifestations.

Among the foods most commonly met with as allergens are milk, egg, fish (not the muscle of fish but the collagen which is contained in fish glue as well), strawberry, pineapple, melon, lima bean, navy bean, green pea, corn, celery, spinach, wheat, rice, rye and oats.

Drug idiosyncrasy so-called is nothing more or less than drug allergy. The reaction that occurs in hypersensitive individuals is characterized by the very same phenomena of allergy that we have already described and bears no relation whatsoever to the usual pharmacological action of the drug. No matter how large a dose of quinine is administered to the normal individual, it will never create in him a subcutaneous edema or an attack of bronchial asthma. No matter how large a dose of aspirin we give to the normal individual, we can never produce these same phenomena. The writer has already reported twelve examples of aspirin hypersensitiveness in which the reaction followed within twenty minutes of the ingestion of five grains by mouth. In one case death ensued from the asphyxia by bronchial edema. In another case there was an almost fatal result in which the life of the patient was saved by prolonged artificial respiration.

The drugs most commonly met with that are responsible for these typical allergic phenomena are quinine, aspirin, coal-tar products and morphin. In some instances, the drug reaction manifests itself more particularly upon the skin, and in some instances upon the heart, causing prostration and collapse. My own experience with these drug reactions has led me to be extremely cautious and to warn others against the administration of drugs to which the patient himself objects, for this is sometimes done on the supposition that the patient is purely neurasthenic.

III. BY ABSORPTION FROM INFECTIVE FOCUS. That bacterial proteins or toxins can be absorbed from an infective focus and act as allergens in the strict sense of the word is a matter of great question today. The importance of associated infections, however, in many cases of hypersensitiveness is a thing about which there is no doubt and has a very

important clinical and therapeutic significance. In practically all of the chronic allergic reactions in the nasal and bronchial mucous membrane there is a secondary infection which plays an important role and this will be considered under Therapy.

IV. BY SUBCUTANEOUS OR INTRAVENOUS INJECTION. Therapeutic sera or drugs are very commonly admitted today by both of these routes. If an individual should be hypersensitive to any of the substances so given a serious or even fatal result would immediately take place. It is always necessary therefore either to make a cutaneous diagnostic test or in the case of drugs resort to preliminary medication by mouth in order to make sure of the fact that the patient is not hypersensitive.

In general then it can be stated that those substances absorbed by inhalation usually give rise to symptoms in the upper respiratory tract. Those substances absorbed by ingestion usually give rise to symptoms referable to the mouth, esophagus, stomach, intestine or skin. The determining factor in the localization of the reaction is not known. There is no explanation for the fact that one case will have hay fever alone, while a second will have hay fever with asthma from the same pollen, and a third will have asthma alone or with a minimum of hay fever. Further, in practically all of these cases where the clinical symptoms are manifested strictly locally in the nose or in the bronchi, there is at the same time an associated hypersensitiveness in the epithelial cells which does not show itself clinically in asthma or hay fever, as the case may be, or by urticaria, or erythema, or angioneurotic edema, because the allergen is never absorbed into the blood stream and never reaches these reacting cells. But this phenomenon is of the utmost importance, for it is made use of in the diagnostic tests now to be described.

DIAGNOSTIC TESTS. *Cutaneous.* The cutaneous tests are made by the introduction of solutions of such substances as pollens, vegetable powders, animal emanations and foods or drugs into the most superficial layers of the skin by means of a fine hypodermic needle, or solutions of such substances or powders of the same can be applied to small abrasions of the skin. The reactions are positive or negative.

The positive reactions vary in their intensity, depending upon the degree of hypersensitiveness of the individual and are clinically classified as marked, moderate or slight. The marked reactions show within a very few minutes an urticarial wheal which rapidly increases in size and spreads into the surrounding tissue by means of peculiar pseudo-pod projections. Outside of the wheal there is a distinct zone of hyperemia. The moderate reactions show a hyperemic zone and a wheal which increases considerably in size but lacks the pseudo-pod projections. The slight reactions also have a zone of hyperemia with very little increase in the size of the wheal. In negative reactions there is no hyperemia and no development of a wheal.

Ophthalmic tests are also made, especially in cases of coryza and asthma, in order to confirm the findings by the cutaneous method. A drop or two of a solution of the substance to be tested is placed on the caruncula, or conjunctival mucous membrane. Positive reactions are characterized by itching and lacrimation with congestion of the conjunctival and corneal membrane. They are designated as marked when the entire cornea is congested, moderate where half of it is congested and slight where there is only congestion in a single quadrant.

From the standpoint of general diagnosis the cutaneous tests are much more important. From fifteen to thirty of these tests may be made at one time. In the more obscure cases where from one hundred to one hundred and fifty solutions have to be tried, the study of the case will occupy several days. For the interpretation of the reactions this much can be said: That for all cases with a typical history of hay fever of the vernal or autumnal type, the cutaneous tests supported by the ophthalmic reactions are reliable and satisfactory indices in over 95 per cent of the cases. In bronchial asthma it is possible to diagnose approximately 80 per cent of the cases by means of the cutaneous reaction, whereas in urticaria, angioneurotic edema, and the other skin manifestations, not more than 50 per cent can be so diagnosticated today. Further, we find positive cutaneous reactions, especially to foods, in individuals who can eat these foods without any evident clinical reaction whatsoever. Such cases are not rare and we explain this apparent paradox by the assumption that these foods as such, in the process of digestion are so completely altered that they never reach the cutaneous reacting cells. This being the case then we must assume that in those individuals who have a cutaneous reaction for a certain food substance and yet who, on the ingestion of this article, show a clinical reaction such as urticaria, there is some additional factor that permits the absorption of the unaltered substance through the intestinal mucous membrane in order to produce the reaction. What this factor is we do not attempt to explain today. . . . Drugs as a class do not give cutaneous reactions unless an urticaria is one of the clinical manifestations of the ingestion of the drug itself.

On account of the fact that there has arisen so much misunderstanding in the interpretation of the cutaneous tests, it has seemed wise to stipulate two postulates which if they are fulfilled in every case that is studied will make the diagnosis definite and distinct.

I. Hypersensitiveness must be demonstrated either (a) by a positive local reaction, cutaneous or ophthalmic or (b) the original allergic manifestation must be artificially reproduced at will on the introduction of the substance, either inhaled, ingested, or subcutaneously injected.

II. It must be shown that the individual comes in contact in some way with the suspected substance in order to permit it to act as an etiological factor.

I have dwelt thus at length on these preliminaries because they are the foundation or cornerstone, as it were, of the therapy. Let me emphasize here that therapy, wherever resorted to, must be specific. Specificity is the basis of all our conception of these conditions today and a critical analysis of our cases shows that no satisfactory result has ever been obtained by any form of non-specific therapy.

Therapeutics of Allergic Coryza and Bronchial Asthma. These two clinical conditions can be considered together because they are caused by more or less the same types of substances and the methods of treatment are clinically identical.

Asthma or hay fever occurring in the spring, from the middle of May to the middle of July, are caused in practically all cases by the pollen of grasses. The autumnal form of hay fever and asthma is due to the pollen of ragweed in such a large percentage of cases, from 90 to 95 per cent, that the other forms of pollen occurring at this time need be considered only as exceptional instances. Unless an individual can move from the locality where these pollens exist, treatment is indicated. On account of the fact that the vernal grasses exist over all the continents and that an individual is free only when he is on the ocean, treatment is practically always necessitated in the cases of early hay fever and asthma of any degree of severity. Those cases that react to the pollen of ragweed can obtain freedom in Europe, in Florida and California and parts of northern Canada. But unless they can move to some such locality they should be treated also.

In order to treat these cases satisfactorily we first determine not only the fact that they react to grass pollen or ragweed respectively, but additional tests are made with varying strengths of the pollen extract in order to estimate the degree of hypersensitiveness. Patients who show a marked reaction to the extract containing 0.01 mg of nitrogen to the cubic centimeter are exquisitely sensitive and must be given very small doses in comparison with those individuals who only show marked reaction with a solution containing 0.05 to 0.1 mg of nitrogen to the cubic centimeter.

Where this can be done, these patients are treated prophylactically, that is, injections are begun six to eight weeks before the onset of the attack and they are given injections of gradually increasing strength at weekly intervals until within two or three weeks of the end of the season. In other words, in prophylactic treatment, from twelve to fifteen injections are given at weekly intervals. Those cases that are not so treated may obtain very beneficial effects, even though the attack has started, by injections given daily for three or four days, then at intervals of two, three and four days, gradually increasing the intervals and at the same time increasing the quantities until the end of the season. In these cases of phylactic treatment the number of injections given is usually twelve to fifteen.

The writer compared a small series of 135 cases of hay fever and asthma and tabulated the results for each condition as follows:

	Asthma Per Cent	Hay Fever Per Cent
Not improved	5	4
Slightly improved	6	5
Improved	36	85
Free	53	6

This is interesting as showing that the asthma is absolutely controlled more readily than the hay fever, but in general we can state that in at least 80 per cent of the cases, more than 80 per cent of the trouble is removed by treatment, whether prophylactic or phylactic.

Asthma and Allergic Coryza from Vegetable Powders. This is found more particularly in the sachets and toilet powders commonly used. The symptoms are identical with those of pollen except that there is no seasonal variation, the attack depending entirely upon exposure to the irritant. When it is in use by the individual or some member of the family the disturbance resulting from it is chronic. In these cases the diagnosis is sufficient and treatment consists in removal of the irritant. Treatment by injections, as in the pollens is not indicated except in those exceptional cases where the individual is so unfortunately situated that conditions cannot be controlled. Where treatment must be given the same principles hold as already described for the pollens, beginning with minute doses and gradually increasing the strength until a very high degree of resistance is obtained. The difficulty with these cases is that this resistance is not persistent but can be maintained by injections given at intervals of one or two months over a long period of time.

Asthma and Allergic Coryza from Animal Danders. The same principles hold here as with the sachets. The diagnosis should be sufficient and treatment is only indicated where proper environment cannot be secured.

Asthma and Allergic Coryza from Foods. These conditions are not particularly common except in children. They comprised only about 2 per cent of our entire series. In such instances, it is better to avoid the articles of diet to which the individual is hypersensitive. Occasionally in children this cannot be done where the individual reacts to many of the important articles, such as eggs, milk, and cereals. In such an instance, treatment by injection is indicated, taking one article of diet at a time and producing a degree of resistance sufficient to enable the patient to eat this article without producing a clinical reaction. It is then wise to advise that this particular foodstuff be used daily in certain specified quantities in order to maintain this degree of resistance until such time as nature has caused the

reaction to be outgrown. . . . These reactions in children, as a rule, disappear by about the age of puberty.

Asthma and Allergic Coryza from Drugs. Here the diagnosis is sufficient and avoidance of these drugs is absolutely essential.

Asthma and Allergic Coryza from Bacterial Proteins. All cases of chronic allergic coryza and asthma have an associated bacterial infection which is best treated by the use of autogenous vaccines, and this irrespective of the fact that they do not show typical cutaneous reactions to a solution of the protein itself.

The other forms of hypersensitiveness, such as urticaria, angioneurotic edema, erythema, eczema and the gastro-intestinal manifestations, are, diagnosticated in only about 50 per cent of the cases and practically all of this fifty are due to ingested articles, either foods or drugs. The diagnosis is a sufficient indication of the therapy which is merely an avoidance of the reacting factor.

It will be evident at once that in this therapy there is, with the exception of food reactions in children, nothing whatsoever in the nature of a cure. A result satisfactory to the patient is obtained by avoiding the source of trouble, but in no way can we today produce any permanent resistance or desensitization at will, for there is an inherited constitutional characteristic that, as yet, Nature alone knows how to cure.

To sum up, then, the important points . . . are these four: (1) That animal anaphylaxis is not identical with human hypersensitiveness or allergy; (2) that in our thoughts of human hypersensitiveness we must discard the conception of a protein reaction as too restricted, for human allergy can and does exist toward many non-protein substances, particularly the drugs; (3) that careful and accurate diagnosis is essential for any therapeutic procedure or advice; and (4) that treatment of a specific nature, when resorted to, does not produce a permanent resistance, for we cannot alter the inherited constitutional characteristics. The results to the patient, however, are none the less satisfactory, even though sometimes slightly irksome.

THE USEFUL APPLICATION OF CLINICAL KNOWLEDGE

Knowledge that is to be applied usefully to the health of mankind will almost always come by a series of steps, the first of which is the application of a test directly to the human problem. It is in the nature of things, however, many steps may intervene, that the first and last must be clinical; as it is also in the nature of things that almost all important physiological discoveries that are immediately applicable to the treatment of disease have their original source in clinical observation.—Sir Thomas Lewis.

Progress in Allergy

ENZYME LYSIS OF ASTHMATIC SPUTUM

A Review and Progress Report

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Interest in the possible use of lytic enzymes to dissolve the thick tenacious sputum of the asthmatic patient has long been present and was a natural outcome of the laboratory use of enzymes to thin tuberculous sputum. However, *in vivo* use of lytic enzymes has come about only in recent years since purified enzyme products have become available for investigation and clinicial trial.

FACTORS INVOLVED IN SPUTUM VISCOSITY

An understanding of the structure of sputum and the factors involved in its viscosity are helpful in determining the type of enzyme which could be the most effective lytic agent for a particular case.

Blanshard[1] in his article, "Viscometry of Sputum," points out that viscosity of bronchial secretion is mainly due to its fiber structure. These fibers are of two types: mucoprotein fibers and desoxyribonucleoprotein fibers. The mucoprotein fibers predominate in mucoid sputum secreted by the goblet cells in the bronchial mucosal glands, and in the mucus secreted by the submucosal glands. The desoxyribonucleoprotein fiber is a degradation product of the polymorphonuclear leukocytes, and therefore it predominates in purulent sputum. An additional factor in sputum viscosity is the fluid component of the bronchial secretion which originates from the same sources as the fibers but with some amount added by transudation from the pulmonary vascular bed. Blanshard believes it is a diminution in the fluid component which is responsible for the increased viscosity of over-night sputum, and that this diminution is a result of a combination of a decreased night fluid intake and the diminished pulmonary blood flow with its resulting less transudate from the pulmonary vascular bed.

Inflammation of the bronchial mucosa itself is a factor in producing a particular type of sputum. Where there is no or little infection, mucoprotein fibers predominate; whereas with secondary infection, the desoxyribonucleoprotein fibers predominate. Levine[2] gives a most excellent summary of the entire problem of sputum liquefaction, including a thorough discussion of humidity factors, expectorants, and enzymes.

The possible effect of a variation in the pH of the bronchial secretions on the viscosity of sputum, especially purulent sputum, is suggested by the report of Sherry, Tillet and Christensen.[3] They noted the effect of varying the pH of purulent samples of a pleural exudate containing a high percent of desoxyribonucleoprotein fibers. These fibers were not soluble in water, normal saline, or 0.1 N HCl, but were readily soluble in 0.1 N NaOH, forming a viscid solution. On returning the pH to neutral, the fibers reformed.

Besides NaOH, an enzyme, desoxyribonuclease, which is produced by both streptococci (streptococcal dornase) and by the pancreas (pancreatic dornase), is capable of causing the dissolution of the desoxyribonucleoprotein fibers. Sherry, his associates, and others[4-8] found that lysed purulent exudates contained this enzyme produced by the streptococci which was responsible for the lysing of the desoxyribonucleoprotein fibers. The action of dornase is to depolymerize the nucleoproteins.[8]

Another enzyme, streptokinase, is like streptodornase, produced from streptococci, but differs from it in that it does not affect desoxynucleoproteins or mucus although it will dissolve fibrin.[4]

Salomon, Herschfus, and Segal,[9] in 1954, in a discussion on the use of aerosols of pancreatic dornase, give an excellent summary of the properties of dornase; and Cliffton[10] in 1956 gives a historical review of its therapeutic use which will be discussed later.

It becomes apparent from the composition of sputum that the enzymes capable of thinning asthmatic sputum fall into five general types:

1. Mucolytic—such as trypsin or lysozyme.
2. Anti-purulent or desoxyribonucleolytic—such as dornase.
3. Anti-inflammatory—such as trypsin, chymotrypsin, and streptokinase.
4. Anti-edematous—such as hyaluronidase.
5. Bacteriolytic—such as lysozyme.

BACKGROUND OF INVESTIGATION IN THERAPEUTIC USE OF ENZYMES

Investigations in the therapeutic use of enzymes in respiratory conditions have largely involved trypsin, although L. Unger,[11] in his 1953 report on aerosol trypsin in inflammatory chest conditions, mentions that he and Andrews in 1937 tried an aerosol made from a proteolytic extract of the papaya fruit. The small group of asthmatic patients given the aerosol developed severe local irritation, including bleeding and hoarseness.

In 1947, following Karl Meyer's report on the relationship of lysozyme to gastric ulcer,[12,13] I became interested in the bacteriolytic and mucolytic enzyme, lysozyme, and after some *in vitro* and animal investigations,[14] used an aerosolized solution of crystallized lysozyme on a number of asthmatic patients. Results were disappointing, and side effects included throat and chest irritation.

During this period, most of the work with enzymes related to the effects of local instillation in empyema, abscess cavities, and wounds, using solutions of streptokinase, streptodornase, lysozyme, and trypsin.[3-11,15-20]

TRYPSIN

Although intravenous trypsin was first used in 1911 by W. Baetzner[21a] for tuberculous lesions of the bones and joints and soft tissues, the first clinical use of the crystalline form of trypsin was reported in 1950 by Reiser, Roettig and others,[17,18] who used it locally to debride necrotic areas, and intrapleurally to clean out empyemas. Shortly thereafter, in 1951 and 1952, investigation with trypsin was undertaken in several directions almost simultaneously, by intravenous, intramuscular, and aerosol routes.

It should be mentioned at this point that most of the clinical reports on the use of enzymes in asthmatic type patients must, by their very nature, be largely uncontrolled and based on judgments of the investi-

gator or patient himself. As Cohen and Dwyer[22] point out in their report, it is extremely difficult to conceal the use of a new agent unless the double blind technique is used; furthermore, patients are prone to exaggerate the amount of sputum brought up. Cander and Comroe[23] found that there was a considerable degree of spontaneous variation in pulmonary function study results from day to day. They concluded that pulmonary function studies are of questionable value in assessing results of treatment in patients with bronchitis except immediately after the use of bronchodilators. Such observations as these lay stress on the importance in research of the clinical judgment of experienced observers in establishing relatively objective evaluations.

Probably the most active of all the investigators have been Innerfield and his associates who have contributed many laboratory and clinical reports. Others prominent are Lawrence Farber and his associates of California, and in the clinical field, N. Silbert and H. Golden.

In 1952, Innerfield, Schwarz and Angrist[24] reported good results with trypsin given intravenously to dissolve blood clots in thrombophlebitis. Subsequently in 1953, these authors followed with an omnibus report[25] on the use of intravenous trypsin in 538 cases of all types of acute inflammation, among which were seventy-six cases of chest disease with diagnoses ranging from pneumonia to emphysema, all of which, or 100 per cent, were stated to be definitely improved clinically.

Other papers on intravenous administration of trypsin were also published at the same time.[26] In 1954, Taylor, Overman, and Wright[27] demonstrated that intravenous trypsin when given to rabbits in large enough amounts to change the clotting mechanism, produced intravenous clotting, and hemorrhagic and focal necrosis in the heart and diaphragm muscles.

It is interesting to note that the literature does not record any extensive clinical use of intravenous trypsin after 1954.

AEROSOL TRYPSIN

The aerosol administration of trypsin in an attempt to lyse bronchial secretions was first reported in 1952 by Limber, Reiser, Roettig, and Curtis.[28] After trying the trypsin aerosol on animals without apparent harm, they used it on tuberculous patients to help loosen the sputum with, in general, good results and only some hoarseness and sore throat as side reactions.

In the same year Roettig and Reiser in conjunction with Hobeck and Mark,[29] reported on the use of aerosol trypsin in fifteen patients with chronic chest conditions, ten of whom responded with clinical improvement. Also in the same year, Farber and his associates[30] were the first to report on a possible permanent harmful effect on the bronchial mucosa from the administration of aerosol trypsin.

While clinical improvement with trypsin alone was not significant, they did observe dyskeratosis and atypical metaplasia as demonstrated by cytological examination of the sputum. These findings were amplified further in 1954, in their report[31] on the use of aerosols of trypsin alone and with desoxyribonuclease. Trypsin alone had little effect, but combined with desoxyribonuclease, was quite effective. Side effects were sore throat, cough, asthma, chills and fever, and rash. Marked alteration of epithelial cells, consisting of atypical metaplasia and dyskeratosis, were observed in twelve of sixteen patients receiving trypsin alone or in com-

bination with desoxyribonuclease. These abnormalities persisted even after six months, and kept increasing. No patient received desoxyribonuclease alone in this study.

Another report on the cytological changes in the bronchial mucosa associated with aerosol therapy was made in 1954 by Habeeb, Reiser, Dick, and Roettig.[32] One hundred and fifty-two patients with chest conditions of all varieties, including pulmonary tuberculosis and bronchiectasis, were treated with aerosol trypsin. Close to 100 per cent of all patients improved, with 5 per cent having side effects of dyspnea, chill, and fever. The usual irritations of the throat and respiratory tract were reduced by increased care in rinsing out the mouth, and by proper aerosolization which avoided large size droplets.

Perhaps the greatest boost to the further trial of aerosol trypsin in respiratory diseases associated with thick sputum was the 1953 reports in the *Journal of the American Medical Association,* and in the ANNALS OF ALLERGY by the Ungers.[11,33] They used crystalline trypsin aerosol in seventy-three chest cases of various types and got excellent results in fifty-three. Their failures were mostly in patients with chronic asthma and emphysema, and some with acute asthma. Much of their good results and lack of a significant amount of the usual side effects of sore throat, hoarseness, and increased asthma must be attributed, in my opinion, to the exceptional team work of a large group of skilled technicians. My own clinical trial of aerosol trypsin,[14] which followed the Ungers' papers (1953), confirmed the disappointing results in chronic asthma and emphysema, nor was the respiratory tract irritation resulting easily avoided with the equipment and help available in most general hospitals.

Many other papers on aerosol trypsin therapy were published during that period. Prince, Etter, and Jackson[34] in 1954 reported disappointing results as far as loosening of sputum was concerned in asthmatic patients with either primary or secondary bronchitis; one patient's asthma was made worse. Also Yates and Goodrich[35] found that in seventeen patients with acute and chronic lung disease, ten were markedly improved and two were moderately improved; two patients with status asthmaticus were made worse.

J. F. Craven,[36] in 1953, reported he was able to save the life of a four-year-old child by use of aerosol trypsin treatments, this child being too ill from an obstructive atelectasis, due to a bronchial plug, for bronchoscopic treatment to be attempted. He had previously attempted streptokinase and streptodornase aerosol with little effect, but after two aerosol treatments with crystalline trypsin, there was rapid expansion of the collapsed lungs. Also, in 1953, Varga and Wild[37] reported much help in relieving respiratory complications of bulbar poliomyelitis with aerosol trypsin. However, unlike S. M. Farber *et al,*[31] their preliminary cytological study of the bronchial secretions showed no increase or abnormal metaplasia beyond that usual in chronic bronchial disease.

In 1957, Lawrence Alan Farber[38] reported further cytological studies on sputum smears sent to him by S. M. Farber and associates of San Francisco. These sputum smears were taken after exposing twenty tubercular patients to dornase aerosol alone. Here they found no atypical aplasia, and only transient postaerosol eosinophilia in six.

INTRAMUSCULAR TRYPSIN

It seems probable that Innerfield again, following his work with intravenous trypsin, was among the first to use intramuscular trypsin. He reported[39] equally effective results and less side effects with intramuscular trypsin suspended in sesame oil in patients with acute thrombophlebitis, diabetic cellulitis, and leg ulcers.

Around the same time came a report from H. T. Golden[40] on the use of intramuscular trypsin in sesame oil in eighty-three patients with acute inflammatory disorders, thirty-five being "chest cases" with acute and chronic bronchitis and acute and chronic asthma. All of these patients showed moderate to marked improvement. He also cites, in an addendum, two hundred more cases with substantially the same results, and with side effects, in a small number, involving mostly local induration. There were no changes in blood coagulation or prothrombin time.

Culp,[41] in 1955, reported treating two cases of persistent pertussis with trypsin in oil, with the chests clearing by the fourth day, and becoming completely clear by the eighth day.

In 1956, N. E. Silbert[42] reported improvement clinically in twenty-five asthmatic patients with chest pathology of long standing. Nineteen of them showed marked to slight improvement in x-ray studies. There was no effect on the blood or urine. One patient got severe pelvic pain, a pelvic girdle rash, and aggravation of his asthma. Several others had large local swelling and pain at the site of injections. In 1957, Silbert[43] reported on another group of patients with chronic chest disease. Twenty-five patients were given trypsin in oil, and ten, trypsin in aqueous gel. These again all received some improvement—some marked, some less so, even though Vitalometer and x-ray studies were not consistently improved. In addition he noted no correlation between x-ray findings and Vitalometer studies. The Vitalometer studies included calculation of predicted vital capacity, measurement of actual vital capacity, and the percentage of air expelled during each second of expiration.

In 1956, I reported[14] that the use of intramuscular trypsin injections in oil in twenty-one severe asthma and emphysema patients gave marked and even dramatic improvement in eight; the rest were not helped. The improvement seemed limited largely to those patients with a pronounced secondary infectious factor. In addition it appeared that improvement with trypsin showed up after the first or second injection, or not at all. Two children of the group with unresolved pneumonia cleared dramatically with intramuscular trypsin injections when other measures failed. At that time, as with other clinical reports, no evidence was found of generalized allergic reactions, but only the large local inflammatory reactions at the site of the injection in a small per cent.

In 1958, Cohen and Dwyer[22] attempted a more controlled analysis of the effects of intramuscular trypsin. They selected twelve patients with chronic bronchitis, all of whom had dyspnea and wheezing, and difficulty in raising sputum. Prior to the injection of trypsin they recorded the twenty-four hour sputum volumes and pulmonary function studies for four to five days of regular treatment; they then administered trypsin in oil every eight hours for five days. Attempts were made to conceal the use of the new treatment material. In evaluating the results of trypsin treatment, most patients thought they had less sputum, but volume measurements generally showed the same or a slightly increased amount. They found no consistent significant changes in pulmonary function

studies. Local reactions were, as usual, inflammatory swelling at the site of the injection. Cohen was unable to confirm Silbert's findings of almost 100 per cent effectiveness and concluded that, in spite of the smaller group, there was no convincing evidence of the value of trypsin in this type of patient. However, the patients themselves felt they had easier expectoration.

As to more recent reports, in a paper submitted for publication, there will be summarized my own experience with injectable trypsin over the last three and a half years. The total series involves ninety-eight patients selected primarily for lack of response to the usual medications. Most of the patients had asthmatic type symptoms with secondary infection as a prominent preceding or concommitant factor. The materials used included trypsin and chymotrypsin in their various forms. No essential difference was found between trypsin and chymotrypsin, either in effectiveness or in tendency to side effects. Of ninety-eight patients treated by injections, twenty-eight received marked relief with marked loosening of sputum and marked lessening of dyspnea; eight of these twenty-eight, which included three cases of unresolved pneumonitis in children, had remarkable and dramatic relief. Nineteen had moderate relief with some loosening of sputum; and fifty-one had no relief. Contrary to all previous reports, marked allergic reactions can occur with trypsin and chymotrypsin. Of the ninety-eight patients, seven had severe reactions; all had severe swelling of an entire extremity; three of these seven had severe dyspnea and wheezing; and one had both severe asthma and generalized hives. All of those with severe reaction had more than five injections of trypsin or chymotrypsin. Switching from chymotrypsin to trypsin or vice versa would in some cases diminish the reactions for one or two injections, but subsequently the same severe reaction would occur. Moderate local reactions involving swellings up to five inches occurred in six of the ninety-eight. In general the effectiveness of trypsin or chymotrypsin was most notable in patients with secondary infection, and especially in children with secondary infection. Patients with acute asthma and chronic emphysema were not generally helped.

BUCCAL TRYPSIN

Innerfield again was first to report (1956) on the buccal administration of trypsin to achieve its anti-inflammatory effects.

In regard to the absorption of trypsin from the buccal mucosa, J. M. Miller,[48] in a paper soon to be published, demonstrated, by the use of radioactive tagged iodine, almost immediate absorption of bucally administered trypsin (within one minute and in high concentrations). Thus all four—aerosol, intravenous, intramuscular, and buccal trypsin—can be considered, for practical purposes, to be absorbed almost immediately after administration.

Side effects of buccal administration are most evident from too frequent use of the tablets. The amount of buccal mucosal irritation is a function of the time required to absorb the required dosage,[48] i.e. the more rapid the absorption, the less the irritation. In the asthmatic emphysematous patient where prolonged usage is required, this can be an important factor limiting its use.

In their papers published in 1956, Innerfield *et al*,[45-47] reported a reduction of edema and prompt subsidence of inflammation, especially of traumatic inflammation. In another report involving 141 patients, Inner-

field[49] found that buccal trypsin decreased the viscosity of respiratory secretions in patients with acute and chronic bronchitis, chronic bronchiectasis, unresolved pneumonitis, and broncho-pleural fistula. Attempts were made in this study to record clinical effects more accurately by noting sputum viscosity and the quantity of sputum raised, the extent and and character of cough, the effect upon granulation tissue and vital capacity, and the general systemic effect. They found that long term maintenance therapy with buccal trypsin produced no side effects of any consequence. As usual, Innerfield reported close to 100 per cent success with the one hundred and forty-one patients who had diagnoses ranging from recent trauma or acute inflammation to hematoma, cellulitis, boils, thrombophlebitis, contact dermatitis, and upper respiratory infections. Seven of these had chronic bronchitis, and seven had chronic bronchitis with extensive bronchiectasis.

The trypsin used in the above studies was in the form of 5 mg tablets of crystalline trypsin (later 2.5 mg) and was given every four hours for one or more weeks. The results were satisfactory without any other treatment. Blood tests of clotting systems and other tests showed no evidence of damage or change. Trauma cases showed prompt subsidience of edema, pain, and redness. Patients with upper respiratory infections had prompt reduction in coughing, with easier expectoration and thinning of sputum, and a decrease in the amount of secretion. Side effects were a mild tingling sensation at the site of buccal application which disappeared quickly. Two patients who had sensitivity to intramuscular trypsin also had some soreness in the mouth. Six others with intramuscular trypsin and local inflammatory reactions had no side effects with buccal trypsin. It was Innerfield's conclusion that the results with buccal trypsin were comparable to those from parenteral trypsin.

In 1957, J. M. Miller *et al*[50] also reported on their experience with buccal trypsin in forty-four patients with various inflammatory conditions. They obtained best results from 5 mg tablets four times a day. Only one of the forty-three patients had the side effect of burning sensation of the mouth. No blood changes were demonstrated by laboratory studies.

My own trial of buccal trypsin[44] was limited to a small group of nine patients with asthmatic bronchitis. Only two patients got satisfactory results that bore up under repeated trial. Local irritation did occur, though not marked, but patient acceptance was not enthusiastic. It is possible that a personal lack of enthusiasm for any buccal type treatment in asthma may have influenced the patients' attitude.

A constitutional reaction following the administration of buccal trypsin will be reported by Caplin, Parker, Haynes, and Muelbroek[51] in a paper soon to be published in the ANNALS OF ALLERGY. Their patient developed urticaria, asthma, and vascular collapse following a second buccal trypsin tablet. One injection of Parenzyme had been given previously. Positive immediate skin tests with trypsin, including a positive delayed passive transfer test, were demonstrated. A discussion on the antigenicity of trypsin is included in their report.

ENTERIC TRYPSIN

The most recent form of trypsin is enteric trypsin tablets, developed in the last year.[52] This form of trypsin comes as a 20 mg tablet with a coating intended to delay absorption until the tablet has moved into the small intestine. The aim is to prevent contact of the trypsin with gastric

juices which destroy trypsin. A number of investigators have been working with this form of trypsin in the traumatic field and in the asthmatic field. Their preliminary results are encouraging.[48,53] W. F. Miller of Dallas, Texas, reports thinning of bronchial secretions in six of eight children with cystic fibrosis, and in fifteen patients with chronic asthmatic bronchitis. He also noted accelerated clearing of the pneumonic infiltrate in patients who had delayed resolution of the pneumonic process. N. S. Berger of Scranton, Pennsylvania, noted loosening of plugs in chronic bronchiectasis, and R. N. Smart of Los Angeles, California, reports dramatic liquefaction of sputum in some of his patients with status asthmaticus. M. M. Fenton of Detroit, Michigan, in a personal communication reports moderately successful results in thirty-three patients, with one patient complaining of nausea.

My own experience[44] involves forty patients with asthma and chronic bronchitis and emphysema—all but ten having received other forms of trypsin and chymotrypsin. Of this group, seventeen or 42 per cent had marked relief, six or 15 per cent had moderate relief, seventeen or 42 per cent had no results. Most of those getting marked relief also obtained marked relief from injected trypsin. One patient, a woman fifty five years of age, had a histamine-like reaction with flushing of face regularly one or two hours following the ingestion of each trypsin tablet.

If results with enteric trypsin continue to be comparable to those with injected trypsin, its use certainly would be preferable to the injections, and definitely so, if one wants to avoid local allergic reactions which are certain to occur at some point following repeated injections. For instant absorption, buccal trypsin should be as effective as injections because of the almost immediate high blood levels of enzyme which have been demonstrated. As far as patient acceptance goes, and provided effectiveness is equal, patients should prefer buccal trypsin to injected trypsin, and enteric in preference to all of them!

CHYMOTRYPSIN

Chymotrypsin is another proteolytic enzyme of the pancreas which acts in combination with trypsin to digest proteins in the intestinal tract. It was named for its clotting action on milk.[21b]

Chymotrypsin is activated from its precursor, chymotrypsinogen, by trypsin. Unlike trypsin, chymotrypsin can not activate itself from its precursor, and it is not affected by enterokinase.[21b] Like trypsin, its hydrolytic action is that of a depolymerizer. It also can produce a shock syndrome in animals by appropriate intravenous administration, and can inhibit the development of experimental egg-white edema in rats, as well as increase the permeability of tissues in rabbits. As to its effects on the blood coagulation system, while chymotrypsin does not clot blood,[21c] in large doses, either *in vivo* or *in vitro*, it leads to a prolongation of the clotting time, a marked increase in the prothrombin time, and a diminution of the plasma fibrinogen levels.[21d]

It has been maintained by the manufacturers of chymotrypsin that it is superior to trypsin in that it produces the same results as trypsin, but without the harmful effects on the blood coagulation systems and the danger of clotting, besides giving less pain on injection.[54-56]

Clinically speaking, such a claim means little, since in the small doses required for clinical effect, there is no change in the blood coagulation systems by either trypsin or chymotrypsin.[21j] All the harmful effects

noted in the literature are from intravenous administration at a rapid rate in exceedingly high dosages in animals, or from aerosol administration in man.

Extensive clinical trial has shown no apparent differences between trypsin and chymotrypsin in results, or in allergic reactions, local or general.[21a,44] It appears that for practical purposes, trypsin and chymotrypsin can be considered identical. While they each have their own specific antigenicity, there is a high degree of cross reaction as shown by the development of local allergic reactions with chymotrypsin, after a few injections, in those patients having large local reactions to trypsin.[44]

One of the few direct reports on the uses of chymotrypsin in asthma, bronchitis, rhinitis, and sinusitis, is by Parsons[57] in 1958. Sixty chronic cases, 10 per cent of whom were children, were treated with 5000 units per cc of aqueous chymotrypsin. The addition of chymotrypsin to other routine treatment resulted in marked improvement in 75 per cent. Subsequent treatments were just as effective. Only one patient had a large local reaction, eight inches in diameter, at the site of the injection.

From a personal experience with over 500 injections of various forms of trypsin and chymotrypsin, there seems to be one small advantage that aqueous chymotrypsin (in a saline solution) has over aqueous trypsin (in a 5 per cent denatured gelatin solution). With aqueous chymotrypsin, while there is a greater immediate stinging sensation from the injected solution, this subsides quickly. However with the aqueous trypsin, though there is much less immediate stinging sensation, a stinging pain may come on within a minute or two and may last for a considerable time, at least several minutes, and then persist longer as a dull aching. Evidently trypsin is locally somewhat more irritating than chymotrypsin, and evidently the gelatin does act to limit the immediate irritating effect of trypsin.

MECHANISM OF ACTION OF THE ENZYMES, TRYPSIN AND CHYMOTRYPSIN

Much has been written about possible indirect action of trypsin and chymotrypsin through activation of other enzyme systems. Martin[21e] postulates a direct action based on the fantastically small concentration of enzymes present in the body. A third possible effect is through a change in the balance of the inhibitors of the enzymes and the enzymes themselves. In essence, one can say there is no valid evidence for any of the proposed mechanisms, and that most likely all three take part in the total effect produced.

Clinically, it can be stated that trypsin reduces viscosity of inflammatory exudates and facilitates drainage with re-establishment of normal circulation.[21f] If there be any differences between trypsin and chymotrypsin, clinical use demonstrates no therapeutic differences with the current dosages employed.[44]

The disparity between the dosages of trypsin used in aerosol treatment and parenteral treatment is discussed by Innerfield.[46] He points out that whereas 100 mg of trypsin is needed with aerosol treatment, parenteral and buccal use require only 2 to 5 mg. The difference, he postulates, is due to a direct enzyme-substrate interaction with the aerosol trypsin, where the extent of protein substrate depolymerization is a direct function of the quantity of enzyme introduced. Parenteral enzymes, because of the relatively minute amounts absorbed, must surely act by "activation of patient's own proteolytic enzyme system" and by conversion of the precursor "plasminogen" into the active enzyme "plasmin." Thus with

parenteral trypsin, the result is a plasmin-protein substrate interaction, unlike the trypsin-protein substrate interaction with aerosol trypsin.

Martin[58] believes that the physiologic role of trypsin is related to a dynamic equilibrium between proteolytic enzymes and protein macromolecules. In much the same words, Innerfield's studies[59] suggest that an impaired proteolytic enzyme-protein substrate equilibrium is one of the fundamental disturbances in inflammation.

ANTIGENICITY AND CLINICAL SENSITIVITY OF TRYPSIN PREPARATIONS

Antigenicity of enzymes has been demonstrated, though it is not marked[21t] and clinical sensitivity is not frequent. The distinction between anaphylactoid and anaphylactic reactions is not easy to determine, but anaphylactic shock has been demonstrated in animals where the dose of enzyme is markedly larger per weight unit compared to human dosages. In human beings, while early reports by Slepian[60] showed no demonstrable antibodies after intravenous trypsin, definite clinical anaphylactic reactions, involving urticaria, asthma, and shock, and positive immediate skin tests, have occurred, as reported by Caplin, and in my own experience. Repeated injections will, in many cases, result eventually in tremendous local swellings with severe indurations and inflammation and eventually generalized reactions.

The comparatively small percentage of allergic reactions encountered with enzymes may be explained by the ability of the enzyme to destroy much of its antibody before fixation. Once the enzyme is fixed to its antibody, its proteolytic functions are inhibited.[21t]

DESOXYRIBONUCLEASE

Desoxyribonuclease is also a depolymerizing enzyme found in the pancreatic secretion but more limited in its action which is specifically on desoxyribonucleic acid.[9,61,21k] It therefore does not have any intrinsic proteolytic action of its own.[21l] However, in its impure form, such as streptodornase or pancreatic dornase, it usually contains various amounts of the proteolytic enzymes. Besides in the pancreas, desoxyribonuclease is also found in other tissues and in organisms other than animals.

The most common sources of desoxyribonuclease are from the pancreas (pancreatic dornase) and from streptococcus cultures (streptodornase). In the latter, it is secreted by the streptococci along with streptokinase, hyaluronidase, ribonuclease, and enzyme-inhibiting substances.[4] Streptokinase, unlike streptodornase, has no proteolytic or mucolytic action and acts only to effect the dissolution of blood clots and fibrinous exudates.[62] Clinically, desoxyribonuclease can be obtained, combined with streptokinase, for intramuscular injection and in the form of buccal tablets, and in a relatively pure form as "pancreatic dornase" for use as an aerosol.[63]

As has been mentioned previously,[3] a large part of the viscosity of purulent exudates is due to desoxyribonucleic acid fibres derived from the nuclei of the pus cells. The lessening of this viscosity is the result of the action of the desoxyribonuclease on these fibres.[1,3,5,6,8] The effective action of desoxyribonuclease takes place almost immediately on mixing with the purulent substrate.[5,6,63]

Lyophylized pancreatic dornase in saline at room temperature retains activity for six to eight hours. It is not affected by antibiotics. Any fibrinolytic activity pancreatic dornase may have is due to the small amounts of trypsin and chymotrypsin it contains. In contrast to strepto-

dornase, which is mechanically labile, the activity of pancreatic dornase is not lessoned by aerolization.[61]

In the clinical field, Armstrong and White in 1950, first reported[62] the successful treatment of viscous purulent exudates with desoxyribonuclease. In 1954, Salomon, Herschfuss and Segal[9] reported treating thirty-six patients with chronic bronchial asthma, chronic pulmonary emphysema, bronchiectasis, lung abscess, pneumonia, and atelectasis by aerosols of 50,000 to 100,000 units, one to three treatments daily. They combined pancreatic dornase with intermittent positive pressure treatments and got better results than with Vaponefrin® alone. All patients brought up more sputum within one-half hour, and cough was easier and more productive. There were no side reactions as was reported with aerosol trypsin, and no allergic reactions. Cytological studies of sputum showed no abnormal cells.

Farber *et al* reported[30,31] that the combination of dornase with trypsin aerosol was much more effective than trypsin alone, but that atypical cytological change in bronchial mucosa persisted.

Cliffton, however, set out to evaluate purified pancreatic dornase in all pulmonary conditions unresolved by standard procedures.[10] Local and general effects were observed and noted by clinical and laboratory means, and by bronchoscopy and pathological examination of resected specimens. He used 100,000 units dornase in two cc of diluent. In all, one hundred and four patients were treated. Among these were sixty-five prebronchoscopy cases who had aerosol treatment prior to bronchoscopy and who showed a normal mucosa afterward, confirmed by biopsies.

Thirty-nine of the patients were seriously ill with severe chronic chest disease. There was a loosening of secretions and cough, and an increase in the quantity of sputum after the first treatment. Subsequently, there was less sputum. There were no generalized reactions, though two patients had sore throats, and two, nausea and vomiting. Cellular studies and biopsies showed no reaction. Two asthmatics had no help. Those patients with acute pulmonary diseases, such as atelectasis secondary to mucus plugs or thick tenacious sputum, responded most rapidly; those with chronic disease less well, or poorly. Repeated inhalations led to no irritation.

Reports on the parenteral administration of desoxyribonuclease are very scanty. However, in the literature on pancreatic dornase put out by Sharp and Dohme,[63] they caution against parenteral administration. Intravenous administration of pancreatic dornase was reported to be safe by Johnson *et al.*[21j] Miller *et al*[21g] reported streptodornase had no anti-inflammatory action in their patients.

It seems that dornase deserves more investigation and trial in aerosol treatment of purulent chest disturbances, for there is some indication that it has less irritating effects than trypsin. For status asthmaticus conditions associated with secondary infection and thick plugs, it would be worth the slight added risk to use it combined with trypsin for aerosol treatment. It would also appear that pancreatic dornase would be more effective than streptodornase in these conditions due to its added content of traces of trypsin and chymotrypsin, and to its resistance to mechanical breakdown.

STREPTOKINASE

Streptokinase is a protease found in streptococcal culture which acts indirectly upon a substrate of fibrin or fibrinogen by activating plasmino-

gen to form plasmin. It is plasmin which produces the lysis of fibrin in the inflammatory barrier about an area of infection. It has been demonstrated by Tillett *et al*[64,21i] in 1955, and recently by Johnson *et al*[65] that intravenous administration of streptokinase causes lysis of fibrin. Most of the recent work with streptokinase has been with buccal administration which showed equally effective antifibrin and anti-inflammatory effects.[66,67] These studies used the commercially available combinations of streptokinase and streptodornase.[66-68] Pertinent to this progress report is the statement by Innerfield *et al*[67] that buccal streptokinase-streptodornase in patients with acute or chronic respiratory tract infection leads to thinning and loosening of their thick tenacious stringy secretions, just as with trypsin; and that it provides a safe and effective means of reversing inflammation with no or little side effects. Three patients with bronchiectasis had good results, and nine with chronic bronchitis, excellent to good results.

Caution is urged regarding the use of streptokinase in patients with defects in clotting mechanisms, or with abscesses; and concommitant use of antibiotics is stressed.[66]

A limited regional survey of the use of Varidase®[68] buccal tablets seems to indicate that the administration of this tablet for longer than four to five days, t.i.d., leads to irritation and ulcers in the mouth. The trend of hospital orders now is to prescribe them intermittently, four to five days on, t.i.d., then three days rest, and then another period of four to five days of the tablets.

LYSOZYME

At present there is no report in the literature on the use of the mucolytic and bacteriolytic enzyme, lysozyme, to help lyse asthmatic sputum. In 1947, my attention was drawn to lysozyme following a report by Karl Meyer and his associates[12,13] at Columbia University detailing the theory that a possible cause of peptic ulcer was an overproduction of lysozyme in the stomach of ulcer patients, and an increased production of it during emotional upsets.

Lysozyme is a bacteriolytic enzyme discovered in 1922, by Sir Alexander Fleming, the discoverer of penicillin, while investigating the lysis of bacteria in nasal mucus. Lysozyme is present in tears, saliva, and in a number of animal tissues and fluids, the richest source being hen's egg white. Its concentration in the serum is insignificant—about 0.01 per cent. There is ample proof of the ability of lysozyme to dissolve mucin by breaking down the complex polysaccharide portion of mucin.[69-72]

It should be noted that lysozyme derived from egg white has been shown to be antigenic and the possibility of allergic reactions to it must be considered.[73]

As reported elsewhere,[14] in 1947, a number of *in vitro* experiments using solutions of crystalline lysozyme and asthmatic sputum were performed by me to determine the optimum pH and optimum concentration for lytic action of lysozyme on the sputum. In addition, prolonged exposure of a hamster to high aerosol concentration of the lysozyme showed no macroscopic or microscopic changes of the bronchial mucosa. Subsequently, the trial of an aerosol of a 2 per cent lysozyme solution on seven patients with severe asthma and emphysema gave disappointing results and some evidence of local irritation. However, because of its

definite mucolytic properties, lysoyzme should be worthy of further investigation for its possible value in bronchial conditions in which sticky mucus acts in an obstructive manner.

HYALURONIDASE

One of the enzymes potentially promising as an adjunct in efforts to loosen sticky bronchial secretions is hyaluronidase. Although acting primarily on the mucopolysaccharide hyaluronic acid, it may also hydrolyze other mucopolysaccharides.[21m] The action of hyaluronidase on hyaluronic acid leads to a decrease in viscosity and inhibits the formation of complex protein hyaluronates. Hyaluronidase has, of course, been shown to increase tissue permeability, and to decrease the viscosity of vitreous humor and synovial fluids.[21n] The increase in tissue permeability is correlated with a reduction of resistance of the tissues to absorption. One of the end results of hyaluronidase action is an anti-inflammatory effect.[21o] In normal dose levels, this enzyme can be considered essentially nontoxic.[21p]

Hyaluronidase has been shown to be wide-spread in distribution, from bacteria to all varieties of organisms and body fluids.[21q] It is in especially high concentration in testicular extract; thus, bovine testicular extract is its most abundant clinical source. Hyaluronidase has not been crystallized[21m] and is considered by many investigators as a group of enzymes whose main substrate is hyaluronic acid. Because of its sources and of its relatively impure form, possibilities of allergic reactions to it are more likely than with the crystalline enzymes.

Clinically, hyaluronidase has been used in topical or local administration, rather than parenteral, to increase tissue permeability.[21r] The most effective use so far has been in combination with aerosols of antibiotics in the treatment of tuberculosis, the hyaluronidase serving as a diffusion factor.

Lammers and Herold[74] demonstrated that the inhalation of hyaluronidase produced a liquefaction of necrotic tissue in the lung. An aerosol of hyaluronidase was administered by David and Longueville[75] to a patient with silicosis with improvement in his general condition and reduction in the frequency of cough and amount of expectoration. A. Lass[76] demonstrated increased quantities of antibiotics in lung tissues in animals with no neurotoxic side effects after treatment with aerosols of hyaluronidase and streptomycin. They also treated one human with the combination with a definite increase in serum streptomycin. Subsequently Warnery *et al*[77] treated groups of tuberculous patients with aerosol of hyaluronidase and antibiotics. There was a substantial number of cures. One of the side effects they noted in a small number, among thousands of aerosol treatments, was an intense dyspnea with bronchorrhea.

It is interesting to note that practically all the references in the literature to clinical trial of hyaluronidase in chest conditions relate to European investigations. Two references of especial interest are listed which pertain to bronchial asthma. Unfortunately, neither the original sources nor the translations of these papers by Hajos[78,79] could be obtained. The titles indicate Hajos combined hyaluronidase with hydrocortisone aerosol in treatment of his asthmatic patients.

GENERAL CONSIDERATIONS

There is certainly enough experimental evidence that the proteases are generally anti-allergic in their effect. In animals there has been modifica-

tion and even reversal of the Shwartzman phenomena and also modification of the Arthus phenomenon.[21o,21s]

In a 1959 paper, Innerfield[80] summarizes the physiological and clinical effects of buccally given proteases. He states that the cardinal indication for buccally administered proteases is localized inflammation. He gives no indication as to which of the important proteases, trypsin, desoxyribonuclease, and streptokinase he prefers, though much of his recent work is with streptokinase. All of the physiological effects of parenteral administration are present with buccal administration, and with less side effects.

In general, it can be stated that besides the mucolytic effects of proteases, there is reduction of edema and inflammation in the bronchi and bronchioles, whether due to infection or other causes. Altogether, the uses of the enzymes in bronchial disturbances involving secretion of sticky mucus, edema, and inflammation of the mucosa. should have a beneficial effect in many cases with little danger of harmful effects on the patient from the doses and methods of administration now in use. Aerosol, intramuscular, buccal, and oral routes are all effective, but it is the latter route which should most probably be preferred.

LIST OF ENZYME PREPARATIONS CLINICALLY AVAILABLE

Trypsin:

1. Injectable: (for intramuscular injection only)
   Parenzyme in oil—'National'—trypsin in sesame oil.
   5 mg crystalline trypsin/ml sesame oil
   Parenzyme Aqueous—'National'—lyophilized trypsin in diluent of 5% denatured gelatin and preservatives. 5 mg trypsin/ml
   Tryptar in oil—'Armour'—crystalline trypsin in sesame oil. 5,000 Armour U. proteolytic activity/ml (equivalent to 5 mg trypsin)
2. Aerosol:
   Tryptar—'Armour'—crystalline trypsin
   125,000 Armour U. and diluent
3. Buccal:
   Parenzyme B—'National'
   Each tablet contains 5 mg trypsin
   Chymar Buccal—'Armour'
   10,000 Armor-Units per tablet
4. Oral:
   Orenzyme—'National'
   Enteric coated tablets, each containing 68% trypsin, 30% chymotrypsin, 2% ribonuclease—equivalent to 20 mg crystalline trypsin.

Chymotrypsin:

1. Injectable: (for intramuscular administration only)
   Chymar in oil—'Armour'—chymotrypsin in sesame oil
   5,000 Armour U. proteolytic activity/ml
   (approximately equivalent to 5 mg crystalline chymotrypsin)
   Chymar Aqueous—'Armour'—chymotrypsin in saline solution
   5,000 Armour U. proteolytic activity/ml

Desoxyribonuclease:

1. Injectable: not recommended
2. Aerosol:
   Dornovac—'Merck, Sharp & Dohme'—pancreatic dornase
   Vials of 100,000 U. with 12 cc vials of sterile diluent.

Streptokinase & Streptodornase:

1. Injectable: (for intramuscular administration only)
   Varidase—'Lederle'
   100,000 U. streptokinase and 25,000 U. streptodornase
   20,000 U. streptokinase and 5,000 U. streptodornase

2. Buccal:

Varidase—'Lederle'
Each tablet contains 10,000 U. streptokinase and 2,500 U. streptodornase

Hyaluronidase:

1. Injectable:

Hyazyme—'Abbott'—lyophilized powder in 1 cc vials, each containing 150 and 1500 U.S.P.—T.R.U.
Wydase—'Wyeth'
Alidase—'Searle'
Hyaluronidase injection—'Philadelphia Ampoules Co.'

Lysozyme:

Not commercially available

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DEDUCTIVE AND INDUCTIVE REASONING

Both deductive and inductive reasoning have definite limitations in biology, but the limiting factor is the same for both. The smaller the number of individual observations, the greater the danger that generalizations made from them will not hold true. This limits inductive and deductive reasoning to the same extent. When the, at first unconnected, observations are gradually arranged into a science, actually induction and deduction follow each other and depend upon each other. They are like consecutive steps with the left and the right foot in a walk; it would be quite false to attribute greater importance to one or the other.

Those who object to inductive reasoning do not realize that what they actually deplore is the unwarranted confidence in a general law. To inspire confidence a generalization must be based on as many observations as possible; however, once formulated on the basis of a given number of data, it is no more nor less likely to be correct as a general law than as a guide permitting correct deductions in new particular instances. Of course such deductions cannot be accepted as equivalents of a proof; their immense value lies merely in singling out among the infinite number of possible experiments those few which are worth doing.—HANS SELYE, "How Not to Write a Medical Paper," International Record of Medicine and General Practice Clinics, 168:10 (Oct.) 1955.

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Frank, R. C.: Farmer's lung—a form of pneumoconiosis due to organic dusts. Am. J. Roentgenol., 79:189-215 (Feb.) 1958.
Observations on 27 patients followed up for 6 years. The syndrome developed after exposure to moldy hay silage, or moldy grains. Shredded corn stalks and dust from fresh hay and grain were also responsible.

Ordman, D.: Desensitization to bee stings by intracutaneous injections of whole-bee extract. Brit. Med. J., Aug. 9, 1958.
Successful desensitization is reported of 19 persons, originally highly sensitive to bee stings.

Greisman, S. E.: The role of anaphylatoxin during *in vitro* anaphylaxis. J. Immunol., 81:214 (Sept.) 1958.
Suggests that activation of serum anaphylaxtoxin is a necessary intermediate step causing release of tissue histamine.

Lindsay, D., Prlina, I., Bischoff, A., and Becker, S.: Cutaneous reactions due to sulfamethoxypyridazine, A.M.A. Arch. Dermat., 78:299 (Sept.) 1958.
Of 55 inpatients and 30 outpatients given sulfamethoxypyridazine for urinary tract infections, 10.9% of the former and 12.7% of the latter developed untoward reactions as fever and dermatitis.

Brown, C. H. and Haserick, J. R.: Acute peptic ulcer after triamcinolone therapy. Report of three cases. A.M.A. Arch. Dermat., 78:289 (Sept.) 1958.
Ulcer program recommended in patients with pertinent history.

de Alemquer, M.: Severe hypersensitivity reaction to para-aminosalicylic acid. Am. Rev. Tuberc., 78:462 (Sept.) 1958.
The seven signs of the reaction are fever, exanthema, circulatory collapse, psychic disturbances, jaundice, polyadenopathy, and hematologic derangements.

Adlin, E., Sher, P., and Berk, N.: Fatal reaction following the ingestion of meprobamate. Arch. Int. Med., 102:484 (Sept.) 1958.
Occurred soon after the ingestion of several tablets of prednisolone (2 mg), dried aluminum hydroxide gel (200 mg), and meprobamate (200 mg).

Cleveland, W., and Smith, G. F.: Complications following the use of prochlorperazine (compazine) as an antiemetic. A.M.A. Am. J. Dis. Child., 96:284 (Sept.) 1958.
Four cases of side-effects manifested by spasm of muscles of the neck, face, tonque, and spine.

Kaufman, R., and Janeway, M.: Severe allergic reaction to poliomyelitis vaccine. New York J. Med., 58:2832 (Sept. 1) 1958.
Cause not elicited.

Jaques, R.: Inhibition of anaphylactic shock by oral lipids. Experientia, 14:298 (Aug. 15) 1958.
A single oral dose of some lipis, especially vegetable oils, protects guinea pigs against otherwise lethal anaphylactic shock. The mechanism of action is not known.

Herbertson, S., Porath, J., and Colldahl, H.: Studies of allergens from alder pollen (Alnus glutinosa). Acta Chem. Scand., 12:727 (No. 4) 1958.
A peptide-like fraction 300 times more potent by skin test contains 11 amino acids.

Wilson, R., Farber, S., and Mandel, W.: A new agent of therapeutic value in pulmonary insufficiency and irritative cough. AM & CT., V:9, 567-572 (Sept.) 1958.
Dyspnea was lessened and cough suppressed in 30 emphysematous and in 37 tuberculous patients. Erythema occurred in one and pruritus in another.

Gatling, R. R.: Altered reactivity to epinephrine in the hypersensitive rabbit. J. Exper. Med., 108:441 (Oct. 1) 1958.
The degree of reaction appears to be related to the amount injected and to the degree of hypensensitivity.

Helm, F., and Heyworth, F.: Bronchial asthma and chronic bronchitis treated with hydrocortisone acetate inhalations. Brit. Med. J., 2:765, 1958.
Although some of the "inhaled" hydrocortisone is absorbed, the effective dosage is low compared to that needed in oral corticosteroid treatment.

Herxheimer, H., McAllen, M., and Williams, D.: Local treatment of bronchial asthma with hydrocortisone powder. Brit. Med. J., 2:762, 1958.
In 33 of 45 patients improvement occurred, especially in "dry" asthma. In 34 controls the effects were negligible.

Kile, R.: Oral treatment of pruritic dermatoses with a new antihistaminic compound. Antibiotic Med., 5:578 (Sept.) 1958.
Describes new oral repository technique of controlled, sustained administration of a mixture of phenylephrine, prophenpyridamine, and pyrilamine tannates in 311 patients.

Gorham, E.: Bronchitis and the acidity of urban precipitation. Lancet, 2:691 (Sept. 27) 1958.
Because of air pollution from hydrochloric and sulfuric acid from urban areas, precipitation may show pH values of 4-4.5. Effects on bronchial tissues need evaluation.

Goldberg, L., and Diamond, A.: An appraisal of a new antipruritic: trimeprazine (temaril). Antibiotic Med., 5:582 (Sept.) 1958.
In 160 patients the pruritus associated with dermatitis and systemic disorders was lessened or relieved.

Hammond, E., and Percy, C.: Ex-smokers. New York J. Med., 58:2956 (Sept. 15) 1958.
Improvement noted after cessation.

Rostenberg, A., Jr.: Drug reactions. Postgrad. Med., 24:263 (Sept.) 1958.
The A, E, I, O, U of drug reaction therapy; A represents Avoidance; E, Elimination; I, Immunization; O, Obstructive therapy, and U, Unguental applications.

PAPERS OF INTEREST

Burns, J. H.: The antihistamine compounds. Brit. J. Med., 2:845 (Oct. 4) 1958.
Up-to-date review.

Rogin, J. R.: Dermatitis medicamentosa due to diuril (chlorothiazide). Report of three cases. A.M.A. Arch. Dermat., 78:504 (Oct.) 1958.
No comment!

Zolv, B.: Agranulocytosis resulting from Sandostene. J. Maine M.A., 49:335 (Sept.) 1958.
Agranulocytosis (with recovery) in a patient who had been taking 100 mg daily for 4 months. Drug has been removed from the market.

Schamberg, I. L.: A critical evaluation of the effect of steroid lotions on inflammatory dermatoses. A.M.A. Arch. Dermat., 78:490 (Oct.) 1958.
The base, used as control, did as well as the active ingredient.

Elmadjian, F., Hope, J., and Lamson, E.: Excretion of epinephrine and norepinephrine in various emotional states. J. Clin. Endocrinol., 17:608 (May) 1957.
Active emotion is related to increased excretion of norepinephrine, with or without increased excretion of epinephrine. Passive emotion is related to increased excretion of epinephrine and normal excretion of norepinephrine.

Fries, J. H.: An evaluation of allergenic and non-allergenic incitants of gastrointestinal symptoms. Internat. Arch. Allergy, 12:1-2, 106-112, 1958.
Allergens must be differentiated from non-immunologic incitants. Provocation of gastrointestinal responses to conservative quantities of an ingestant specifies the inciting substance but does not prove an allergic etiology. Symptoms may result from a specific fraction of the food, or from a specific additive.

Sharp, J., Griffith, G., Bunnell, I., and Greene, D.: Ventilation with pulmonary edema. Modern Med., Apr. 15, 1958.
Compliance is low, possibly because bubbles block alveolar ducts.

Sevag, M. G., and Ishii, K.: Drug-induced reversible and irreversible enzyme alterations underlying drug-resistance. Proc. Roy. Soc. ser. B., 149:63-81, 1958.
"An induced cytoplasmic variation might permit survival in an unfavorable environment and the subsequent emergence of a genetically new type adapted to that environment."

McMahon, F., and Gordon, E.: Side-effects noted in treatment with methylprednisolone (Medrol). J.A.M.A., 168:9, 1208-1213 (Nov. 1), 1958.
Of 67 patients and ten healthy subjects, disturbances of the body weight was seen in 40, with obesity in 14. Acne occurred in 9, and mental changes in 8. Twenty-one other side effects are listed.

Henderson, L. L.: Hypersensitivity: Newer methods of investigation. Proc. Staff Meet. Mayo Clin., 33:19, 459-466 (Sept. 17) 1958.
Compulsory reading for every allergist.

Elmes, P., Fletcher, C., and Dutton, A.: Prophylactic use of oxytetracycline for exacerbations of chronic bronchitis. Brit. J. Med., Nov. 30, 1957.
Of 88 patients, 44 received oxytetracycline for one week, and the others took placebo. Although the treated patients lost half as much time from work, the results are statistically regarded as probably due to chance.

Becker, R. M.: A new concept in the treatment of penicillin reactions: use of penicillinase. Ann. Int. Med., 48:1228-1242 (June) 1958.
Forty-six patients with penicillin reactions were treated with penicillinase. Twenty-four of these were treated with intramuscular injections of penicillinase alone, with good results.

Zolov, B.: Agranulocytosis resulting from Sandostene®. J. Maine M. A., Sept., 1958.
Agranulocytosis resulting from Sandostene®. A patient who took the drug in 100 mg daily doses for four months presented agranulocytosis. No other drug was used during this period, and Sandostene was presumed to be the logical factor.

In Memoriam

CLARENCE BERNSTEIN, M.D., F.A.C.A.

Clarence Bernstein died April 23, 1959, at the age of fifty-three years. Those who knew him feel the immensity of this loss to themselves and to the continuous progress of allergy. For the newer members who had never met him, how unfortunate, for they have been denied an everlasting pleasure. Our editor has honored me with the privilege of writing this memoriam. I am awed by this responsibility, for it will be most difficult to catch the spirit, the warmth, the intenseness, and the genius of this unforgettable personality.

As I attempt to delineate the activities that have shaped Clarence Bernstein's life, I am impressed particularly with several of his personal characteristics and also some eventful occurrences. Clarence was blessed with an unusual innate ability. He had a photographic mind that imprinted the most difficult passages at sight which he could recall almost verbatim at will. He overflowed with ideas. His discerning mind was so well disciplined in the scientific method that he could critically aid or destroy new concepts. His extemporaneous discussion of original papers given by fellow members was always a welcome stimulus to enliven the proceedings. His own writings were noted not only for their scientific value, but for their literary brilliance. He was frequently on the scientific programs of the American College of Allergy, and also on the faculty for its graduate instructional programs.

Clarence's "Achilles heel" which probably troubled him even in his youth was a bronchial adenoma. Over the period of years, it gave him recurrent vague symptoms that eluded diagnosis. Because of this, many times he was labeled psychoneurotic by many of his conferees. It was only after numerous bronchoscopies and improvements in technique that the tumor could be visualized. After recovery from a successful pneumonectomy and a rejection by the armed forces in the early part of World War II, he was assigned by Procurement Assignment to the Orlando, Florida, area. Here he practiced for the ensuing years where he earned the respect of his fellow physicians and all those who came in contact with him. In 1956, it became obvious that he was suffering from a recurrent systemic invasion of his original lesion. From then until the time of his death, he fought a gallant but losing battle against his unremittent foe. During this time, he had managed to practice under the most difficult circumstances, being in constant pain but showing a fortitude that is rarely encountered. He never lost patience nor the belief that medical science could conquer his malady. His witticisms helped to buoy up the lagging spirits of those who nursed him. His dying hopes were that the postmortem findings in his case might be of some help to the solution of this puzzling malady.

I have detailed his illness not so much for its medical interest, but because of its importance in shaping Clarence's philosophy of medical practice. Somehow I believe his own experiences in illness gave him a humility and a respect for all of his patients' complaints. No symptom was ever too insignificant. Clarence would check and recheck the minutest complaint before labeling a patient, "No Organic Disease." While he received many a negative report on his patients, not infrequently an obscure lesion was found and brought to view.

In the short span of his medical career and in spite of many prolonged interruptions because of illness, Clarence's accomplishments were prodigious. His scholastic achievements are evidenced by his election to membership in such societies as Phi Beta Kappa, Alpha Omega Alpha, and Sigma Xi.

Clarence was a pioneer in the field of allergy. His interest started with basic research on immunology in tuberculosis with Dr. A. R. Rich at Johns Hopkins University, and continued at the Universities in Chicago, where he did much original work along the line of antigen-antibody relationships both in animals and in human beings. He was a certified member of the American Board of Internal Medicine and in Allergy; an active member of the Chicago Society of Allergy, Institute of Medicine, Central Society of Clinical Research, and a founder member of the Society for Investigative Dermatology. He was a consultant in medicine for the Institute of Psychoanalysis of Chicago. He was a Fellow in the American Academy and the American College of Allergy. He was a member and past president of the Southeastern Allergy Association; a founder and past president of the Florida Allergy Society; a member of the Executive Committee of the American Academy of Allergy from 1955-1958. He was program chairman on the Section of Allergy for the American Medical Association in 1957. He was a member of the American Federation of Clinical Research, the Southern Medical Association, American Association for Advancement of Science, and the Florida Academy of Sciences.

Clarence was a man of tremendous drive and energy, and in spite of a very active medical practice and participation in local and national medical activities, he was still able to devote a good deal of his time to the community where he was an active participant in many prominent civic groups.

Clarence had a strong love for humanity. He felt that it was his moral obligation not only to try to save lives medically, but to prevent them from being destroyed by any future catastrophic war. He believed that the United World Federalists was a way toward this end and he became not only an ardent member but an outstanding national figure in its organization.

In spite of all of these activities, Clarence was a devoted family man and he and his wife, Bobbie, were in love with a "oneness" that was incredible. He is survived by his wife and two daughters, Jill and Toni, whose best inheritance would be that they have retained some part of him.

S. D. Klotz, M.D.

ALEXANDER SOCHACKI, M.D., F.A.C.A.

Alexander Sochacki received his Bachelor of Arts and Medical degrees from the University of Pennsylvania. He interned at the Cooper Hospital, Camden, New Jersey, and practiced as a general practitioner, and later as an allergist for thirty years in Camden.

He was a Clinical Assistant in the Allergy Clinic at Jefferson Hospital and an instructor in allergy at Jefferson Medical College. He worked for many years in the Allergy Clinic of Cooper Hospital, and in his later years headed this Clinic.

Dr. Sochacki was a member of The American Academy of Allergy and the Philadelphia Allergy Society.

He was a hard-working member of the profession, and well thought of by his colleagues, patients, and friends.

Dr. Sochacki was promoted to Fellowship in The American College of Allergists in 1944.

TAX DOLLARS AT WORK IN MEDICINE

The total appropriation given to the national institutes of health by Congress is 400 million dollars. Of this, is assigned to cancer 91 million, mental health, 69 million, heart disease 62 million, arthritis and metabolic diseases, 47 million, general research, 46 million, neurological diseases and blindness, 41 million, allergy and infectious diseases 34 million, and dental health, 10 million.

News Items

POSTGRADUATE COURSE IN ALLERGY

A Postgraduate Course in Allergy will be presented by the University of Tennessee, Memphis, on November 5 and 6, 1959. The course will be devoted to the fundamentals of allergy, as well as to the recognition and management of allergic diseases. Further details may be obtained by writing to the Postgraduate Department, University of Tennessee, 62 South Dunlap, Memphis, Tennessee.

CALIFORNIA SOCIETY OF ALLERGY

Officers of the California Society of Allergy for the year 1959-1960 are as follows:

President.....George Harsh, M.D., San Diego
Vice President.....Hyman Miller, M.D., Beverly Hills
Secretary-Treasurer.....Gardner S. Stout, M.D., San Mateo

NEWS OF FELLOWS

Dr. Mayer A. Green, F.A.C.A., has been appointed Clinical Assistant Professor, Section of Allergy, Department of Dermatology of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

WOMEN'S AUXILIARY ANNOUNCES AWARDS

The Women's Auxiliary of The American College of Allergists announces that again, for presentation at the Sixteenth Annual Congress of the College, two prizes will be awarded for the fourth year.

The Bela Schick Award, a prize of $150 and a Certificate of Award, will be made for the best paper written by an Associate Fellow of The American College of Allergists.

The Clement von Pirquet Award will be made for the best paper (on any aspect of allergy), written by an intern or resident. This paper will also be presented at the 1960 Congress (February 28-March 5). A Certificate of Award will be given, a prize of $75, and in addition, $75 to defray traveling expenses to the convention.

All papers are to be judged by a committee consisting of the Program Committee of the Sixteenth Annual Congress and of members of the Editorial Board of ANNALS OF ALLERGY. Awards and checks will be presented at the annual meeting at Miami Beach, Florida, in March.

WOMEN'S AUXILIARY MEMORIAL SCHOLARSHIPS

The Women's Auxiliary of The American College of Allergists announces that it has contributed to the College the sum of $300 for scholarships to the Instructional Course of the Sixteenth Annual Congress of the College, February 28-March 5, 1960, at Miami Beach, Florida. These scholarships will be awarded in accordance with the order in which applications are received and on the basis of the merit of the application. Physicians who wish to be considered for these scholarships should send their applications to Dr. Giles A. Koelsche, Program Chairman, 102-110 Second Avenue, S.W., Rochester, Minnesota.

NEW YORK ALLERGY SOCIETY

The New York Allergy Society will meet on Wednesday, November 18, Hotel Beekman Tower, 49th Street and First Avenue, New York City. A dinner meeting at 7:15 P.M. will be followed by a scientific session at 8:30 P.M. The program is as follows:

Dr. Frank L. Adler, Associate Member, Public Health Research Institute, City of New York: "Studies on the Competition Between Antigens. Implications for the Allergist."

Dr. Abraham G. Osler, Associate Professor Microbiology, Johns Hopkins School of Hygiene and Public Health, Baltimore: "Anaphylotoxin, Passive Cutaneous Anaphylaxis and Complement. Their Relation to Clinical Allergy."

SOME BASIC SOURCES OF MEDICAL KNOWLEDGE

Medicine learned from a monk how to use antimony, from a Jesuit how to cure agues, from a friar how to cut for stone, from a soldier how to treat gout, from a sailor how to keep off scurvy, from a postmaster how to sound the eustachian tube, from a dairymaid how to prevent smallpox, and from an old market woman how to catch the itch insect.—Oliver Wendell Holmes.

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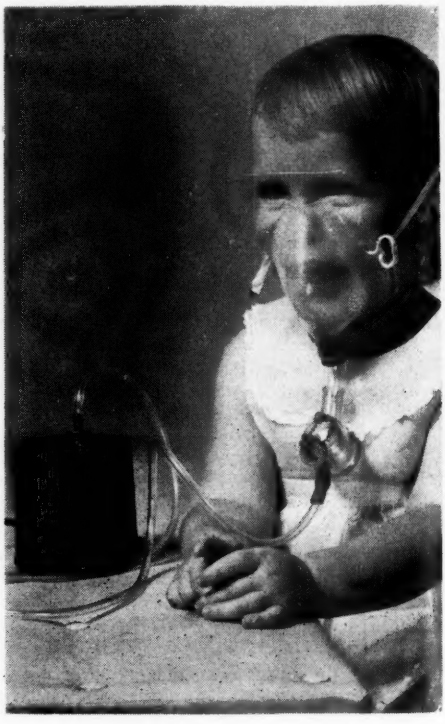

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